FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

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MEETING 69

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NDA 20-766, XENICAL

(ORLISTAT TETRAHYDROLIASTATIN)

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Friday, March 13, 1998

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The meeting was held at the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, at 8:00 a.m., Dr. Henry G. Bone, III, Chairman, presiding.

PRESENT:

HENRY G. BONE, III, M.D., Chairman

JOSE FRANCISCO CARA, M.D., Member

CATHY W. CRITCHLOW, M.D., Member

ROBERT MARCUS, M.D., Member

MARIA I. NEW, M.D., Member

ROBERT S. SHERWIN, M.D., Member

PRESENT (Continued):

JULES HIRSCH, M.D., Member

MARK E. MOLITCH, M.D., Member

JAIME A. DAVIDSON, M.D., Consumer Rep.

RICHARD D. SIMON, D.Sc., ODAC

MATTHEW ELLIS, M.D., Ph.D., Guest Expert

ROBERT SIEGEL, M.D., Guest Expert

KATHLEEN R. REEDY, Executive Secretary

ALSO PRESENT:

ERIC COLMAN, M.D., FDA

KAREN JOHNSON, M.D., FDA

SOLOMON SOBEL, M.D., FDA

BRUCE STADEL, M.D., M.P.H., FDA

TIMOTHY ANDERSON, Ph.D., Hoffman-LaRoche

ARAM CHOBANIAN, M.D., Hoffman-LaRoche

DOUGLAS GREENE, M.D., Hoffman-LaRoche

JONATHAN HAUPTMAN, M.D., Hoffman-LaRoche

MARTIN HUBER, M.D., Hoffman-LaRoche

RUDOLPH LUCEK, Hoffman-LaRoche

JAMES O'D. McGEE, M.D., Hoffman-LaRoche

JAMES SCHLESSELMAN, Ph.D., Hoffman-LaRoche

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:14 a.m.)

CHAIRMAN BONE: Good morning. I'm calling to order the 69th meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

Today we're discussing the NDA No. 20-766 for orlistat or Xenical, sponsored by Hoffman-LaRoche, and we will start by introducing the people who are here at the Committee table, and then the Executive Secretary of the Committee will read the meeting statement.

We will have the opportunity for the open public hearing, and then we'll proceed with the presentations by the sponsor.

All right. If we would actually just start with Dr. Sobel and just go around the table, and if each person will introduce themselves and their affiliation.

DR. SOBEL: Sol Sobel, Metabolic and Endocrine Division, FDA.

DR. COLMAN: Eric Colman, Medical Officer with Endocrine and Metabolic Drugs.

DR. STADEL: Bruce Stadel, Medical Officer, Metabolic and Endocrine Drugs.

DR. JOHNSON: Karen Johnson, Medical

Officer, Division of Oncology Drug Products.

DR. CRITCHLOW: Cathy Critchlow, epidemiology, University of Washington.

DR. DAVIDSON: Jaime Davidson, endocrinology, Endocrine and Diabetes Associates of Texas, University of Texas, Southwestern Medical School.

DR. SHERWIN: Robert Sherwin, Professor of Medicine, Yale University.

MS. REEDY: Kathleen Reedy, Executive Secretary, Endocrinologic and Metabolic Drugs Advisory Committee.

CHAIRMAN BONE: Henry Bone from Detroit, Michigan, Chairman.

DR. HIRSCH: Jules Hirsch, Rockefeller University.

DR. CARA: Jose Cara, pediatric endocrinology and diabetes, Henry Ford Hospital, Detroit.

DR. MOLITCH: Mark Molitch, endocrinology, Northwestern University, Chicago.

DR. MARCUS: Robert Marcus, Professor of Medicine, Stanford University.

DR. SIEGEL: Robert Siegel, Director of the Division of Hematology and Oncology and Chief of

the Cancer Center at George Washington University.

DR. ELLIS: Matthew Ellis, Lombardi Cancer Center, breast cancer oncologist.

DR. SIMON: Richard Simon, biometric research, National Cancer Institute.

CHAIRMAN BONE: Ms. Reedy.

MS. REEDY: The following announcement is the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 United States Code, Section 208(b)(3) and Section 505(n)(4), full waivers have been granted to Dr. Robert Marcus, Dr. Mark Molitch, and Dr. Jules Hirsch. A copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12A30 of the Parklawn Building.

In the event that the discussions involve

any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect of all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

I'd like to state that Dr. Simon is a member of the Oncologic Drugs Advisory Committee and has been screened for conflict of interest, as have all of the members of Endocrine and Metabolic.

Drs. Ellis and Siegel are guest experts and have signed confidentiality statements and have stated their interests, and they have not been such that should be mentioned in a conflict of interest statement.

CHAIRMAN BONE: Thank you, Ms. Reedy.

The next item on the agenda is the opportunity for members of the public to make short statements. This is a unique feature of the drug review process, and it's quiet an interesting one, I think, from the perspective of regulatory authorities around the world actually.

The first statement on our agenda is from -- and I would like each of the people who make statements during this statement to please state any financial relationships to the sponsor or anything of that kind that would be pertinent to the discussion.

The first statement is from Lynn McAfee from the Council on Size and Weight Discrimination.

MS. McAFEE: Good morning.

And we do not accept money from the weight loss industry. So there is conflict of interest.

CHAIRMAN BONE: All right. Everybody has been told they'll get about five minutes, and I'll give you a high sign about half a minute to go.

MS. McAFEE: Please. I wasn't sure if there was a time limit.

The last time I came before you, I pointed out that it was difficult to know what to say about a drug when I had almost no information on it. I'm glad the FDA now has an initiative under consideration that would allow us to speak after the company has made its data presentation.

But now I find myself in the position of knowing a lot about the drug, but knowing nothing about the subject of today's discussion, whether or not this drug can cause breast cancer.

When I first heard about the breast cancer cases I wasn't too concerned because, like others, I couldn't figure out how it could be caused by Xenical since there is such minimal bioavailability. Perhaps it's like having a 100 year flood two years in a row. Statistics are sometimes not truly descriptive of reality. Only perhaps tumor inhibiting properties of certain foods are being excreted preferentially. Perhaps there is a mechanism for tumor growth we simply don't understand yet.

It is your unenviable task today to sort that out. I can only talk about my general feelings regarding Xenical based on the last hearing.

I'm not thrilled by the effect in the profile of this drug. Yes, people lost more weight than placebo alone, and expressed as a percentage, it is significant looking, but certainly not what most people are hoping for, significant cosmetic improvement, but health improvement is the only legitimate reason for approving a drug, not thinner thighs.

There was a ten percent weight loss, which many believe will lead to an improvement in health in those with co-morbid factors, but will this weight loss be maintained?

I have a memory of an effectiveness slide of the entire two-year study. The second year showed people in both placebo and drug groups gaining back weight at nearly the same rate. I don't remember seeing a lot of evidence that the weight those people were keeping off at the end of the second year would stay off.

And if ten percent doesn't stay off, there may not be any health benefit to smaller weight losses. We don't know yet.

Added to the fact that the reported side effects, which were the behavior modification piece of the drug, dropped dramatically in the second year, well, it just makes you wonder.

This does not seem to be a drug that has overcome the weight maintenance mechanism. That would be the Holy Grail, and that would make the risk-benefit analysis very different.

The drug does seem to have a good effect on LDL cholesterol, and that's an important benefit for those who are endangered by high lipids. Other than that I don't see that it has any real health benefit over that expected by the amount of weight lost.

And remember in the majority of fat

people, those who have uncomplicated obesity, these readings may be fine to begin with. My point is that whatever data we see about breast cancer today, this drug does not start out being the greatest thing since sliced bread. I think it may have some usefulness, but not enough to warrant an increase in breast cancer.

I used to be an insurance underwriter. I'm recovered now, but I learned a lot about decision making. One thing I learned is that you underwrite for catastrophic risk much differently than a run-of-the-mill risk. You require more and better information, and you don't take the kind of chances you would in your ordinary book of business.

Any obesity drug should be categorized as a catastrophic risk potential because of the huge numbers of people who would use it, as well as continued uncertainty about the benefits of weight loss.

A lot has been written lately, and even in so august a publication as the New England Journal of Medicine, about the controversy surrounding the issue of mortality and obesity. I would certainly not say that every fat person has the same mortality as every thin person. I think what this issue has brought up

is that there are subgroups of fat people who would be helped by weight loss and subgroups who would not.

Surely very super soft people like myself could benefit from weight loss, but it is unclear whether all of those with Class 1 and perhaps even Class 2 obesity would uniformly be helped by the small amount of weight loss Xenical claims to achieve, assuming again that loss can be maintained.

So the picture is unclear, and that makes it difficult to establish benefit, and I would urge you to proceed on the side of caution. If the drug's approved, I have a lot of concerns about how it will interact in the new reduced fat environment of olestra. When artificial sweeteners were introduced, few people foresaw that they would be so widely used they would be in yogurt, cough drops, and toothpaste.

We have heard that vitamin replacement therapy is necessary with Xenical. Will the use of olestra and Xenical together create additional vitamin deficiencies?

In real life, I expect a significant number of people will use at the same time both Xenical and Meridia and eat as many wild chips as their intestinal tracts can handle. Are there any concerns about interacting with a CNS drug like

Meridia or even phentermine? I would really like to see extensive Phase IV tests on these real life issues.

I'd also like to speak strongly against the use of this in children without some long term studies. I believe I was greatly harmed by my childhood and adolescent use of diet pills. It would be wonderful if Xenical turned out to be a safe and effective treatment for children and adolescents, but until such time as there is evidence of that, I strongly believe this should not be given to children.

No one has ever examined or acknowledged the damage amphetamine cocktails did to fat children of my generation, but I hope the lesson we can learn from the pain of amphetamine children is that extreme caution is needed before prescribing new drugs to children.

I'm sure your participation on the Advisory Committee is often a thankless job, and I know that in the past two years you have been subject to a lot of second guessing by all of us. No matter what your decision is today, and regardless of whether I have agreed with you in the past, I have always respected the effort and caring you put into your decision making.

So I'd like to take this opportunity to thank you for your efforts on our behalf.

CHAIRMAN BONE: Thank you very much.

The next presentation will be by Morgan Downey from the American Obesity Association.

MR. DOWNEY: Thank you, Mr. Chairman.

My name is Morgan Downey. I am a person with obesity, and I am Executive Director of the American Obesity Association.

AOA was founded in 1995 by Richard Atkinson and Judith Stern and a distinguished advisory council as an advocacy organization for the interests of the millions of persons in this country with obesity.

The American Obesity Association is proud to have received support from major pharmaceutical companies, including Hoffman-LaRoche, Knoll Pharmaceutical, Medeva Pharmaceuticals, and American Home Products.

In addition, AOA is supported by over 500 individual dues paying members.

It is the mission of AOA to advocate for public recognition of the epidemic of obesity sweeping through the United States and other countries. We believe obesity is a disease and that weight loss is

the only known therapy.

We endorse patients taking control of this disease as they would any other chronic, life threatening disease. This means being aggressive in managing the disease and its related co-morbidities, and finding support and demanding knowledgeable and compassionate health care, and in engaging in sustainable behavioral changes in food intake and exercise.

According to the latest reports from the Centers for Disease Control and Prevention, about 58 million American adults are over weight to the point where they are incurring health risks. The percentage of American adults with obesity has increased 30 percent in ten years, from 25 percent in 1980 to 33 percent in 1991.

Conservative estimates indicate that 14 percent of children and 12 percent of adolescents are overweight. Thirty-three percent of men and 36 percent of women are overweight.

Obesity disproportionally affects minorities. The prevalence is 48.5 percent for non-Hispanic black women and 47.2 percent of Mexican American women.

The Centers for Disease Control and

Prevention report that the prevalence of overweight in the United States has continued to increase.

To put these figures in context, consider that there are six to 700,000 persons affected with HIV/AIDS in the United States, eight million with cancer, 16 million with diabetes, and 22 million with heart disease compared to 58 million with serious health risks from obesity.

Obesity is the second leading cause of preventable deaths in the United States after smoking. Former Surgeon General C. Everett Koop and others, including the AOA, support the estimate of at least 300,000 premature U.S. deaths a year attributable to poor diet and inactivity, virtual synonyms for overweight and obesity.

For too long the official public health reaction to the epidemic of obesity has been virtual denial. Obesity is shortchanged when it comes to research funding at the National Institutes of Health. It is left out of major public health education campaigns, and it is avoided like the plague by too many health insurers.

The reasons for this society's avoidance and denial of obesity are not the subject of today's hearings. We will leave those for another day. What

we can discuss is the tremendous economic and personal costs associated with obesity and the need to provide positive support for persons engaging in weight loss.

Obesity is a long term, chronic disease. There are at least eight other diseases that worsen as obesity increases or decreases as obesity is treated. They include heart disease, hypertension, dyslipedemia, adult onset diabetes, stroke, sleep apnea, osteoarthritis, and deep vein thrombosis.

If obesity were prevented in the United States, were prevented, the United States could have saved approximately $45.8 billion in 1990 or six percent of health care expenditures. Similarly, 52.9 million days of lost productivity would have been averted, saving employers around $4 billion.

A recent study published in the Archives of Internal Medicine confirms an association between BMI, body mass index, and annual rates of in-patient days, number and costs of out-patient visits, costs of out-patient pharmacy, and laboratory services. Relative to a BMI of 20 to 24.9, annual costs were 25 percent greater for those with a BMI of 30 to 34.9 and 44 percent greater for those with a BMI of 35 or greater.

The author concluded, quote, "Given the

high prevalence of obesity and the clearly elevated disease risks and increased use of health services, there is great potential for reduction in health care expenditures through efforts in weight reduction and prevention of weight gain.

To these economic data must be added the costs and quality of life of persons with obesity. It is hard to think of another condition which inspires as much external stigma and personal shame as obesity. Whether we label it a disease or a condition, there can be no mistaking the toll on personal and professional lives that obesity can bring with or without any co-morbid condition. Many lean individuals have no idea of the self-discipline and effort it takes for many of us just to maintain our weight or to sustain weight loss over a long period of time.

Speaking personally, two years ago I had a BMI of 40. I sought out medical treatment and engaged in an aggressive program. I did not take any medicines, but it was an important security to know that those medicines were available if the program I was in was not able to achieve its success.

During that course of treatment, I was able to start the process of making changes in my

eating behavior and exercise which are still ongoing. While my current BMI of 29 represents an improvement, I have to work constantly to maintain and lower it further.

The American Obesity Association trusts that this Advisory Committee will fully consider the safety and efficacy data on Xenical. Should this product be found to have an acceptable risk-benefit profile, we would hope that it would be promptly approved. Its availability would give millions of Americans hope that they may be able to control their weight and the confidence to consult with their physicians about their weight and health status.

Thank you.

CHAIRMAN BONE: Thank you.

The next speaker is Dr. Barbara Moore from Shape Up America.

DR. MOORE: Good morning. Thank you, Mr. Chairman.

My name is Barbara J. Moore, and I'm here today as President of a not for profit organization called Shape Up America.

Shape Up America was founded in 1994 by former Surgeon General C. Everett Koop to combat the growing epidemic of obesity in America. By way of

disclosure of any possible conflicts of interest, let the record reflect that two pharmaceutical companies, Wyeth-Ayerst Laboratories and Hoffman-LaRoche, are listed among the sponsors of Shape Up America. This means that they provide unrestricted financial support for the educational activities of Shape Up America.

We are not accountable to either company for the educational initiatives we undertake or the materials we produce.

The purpose of my testimony today is to discuss the possible approval of Xenical and the need to accompany that approval with vitally needed consumer and health care professional educational initiatives.

In America, adults tend to grow fatter as they age, and now one out of every three adults is overweight or obese. This weight gain is associated with the development of diseases that I'll refer to as the co-morbidities of obesity: hypertension, Type 2 diabetes, heart disease, certain cancers, osteoarthritis, gall bladder disease, and sleep apnea.

This weight gain is not a cosmetic issue. It is a health issue. For the sake of the public health, we are obligated to do all we can to stop the growing epidemic of obesity and to thereby reduce the

associated co-morbidities.

As a nutritionist whose own area of research interest and expertise is obesity and as a public health professional who has spent years devoted to helping people struggling with weight management, I am well aware of the need for new tools that can help people achieve and maintain a healthier body weight.

Although I have no expectation that pharmacological agents will obviate the need for changes in life style, that is, adopting healthier eating habits and increased physical activity, nonetheless, I view such agents as serving a vital role.

As we develop an increasingly sophisticated understanding of the regulation of food intake and energy balance, we can target pharmacological agents to intervene with normal physiological processes to produce a desired result. In the case of Xenical, that intervention is a particularly interesting one.

Technically speaking, the food that enters the gastrointestinal or GI tract but is not yet absorbed can be viewed as being outside the body. Thus, an agent that interacts with food in the GI

tract and that is not yet absorbed is technically carrying out its function outside the body.

Xenical selectively targets dietary fat before that fat is absorbed into the body. Should Xenical be approved for the U.S. market, it will be the first such agent on the market.

We are eager to have patients who use the drug do so appropriately. Specifically, Xenical functions optimally when the patient consumes fewer than 30 percent of calories as fat. Now, the American Heart Association is a member of the Shape Up America coalition of organizations striving to promote healthy eating and increased physical activity. For years the American Heart Association has advocated that Americans consume fewer than 30 percent of their daily calories as fat.

Shape Up America has taken great care to support this message about low fat eating, as has the U.S. Department of Agriculture and other departments within the federal government. Yet Americans are not doing this. They are typically consuming an average of 34 to 36 percent of daily calories as fat.

Now, I know that Hoffman-LaRoche is as eager as we are to see Americans improve their eating habits by decreasing their fat intake. They want

patients who take Xenical to be successful, and patient success depends on using the drug under optimal conditions.

We want to stem the epidemic of obesity and reduce the heart disease and other co-morbidities of obesity and reducing fat intake serves both objectives.

The appearance of a peripherally acting pharmacological agent like Xenical to treat obesity is an important new development that is welcome, but that carries with it important responsibilities that must be met. We have a responsibility to educate the consumer about healthy eating, especially the importance of consuming a diet that is lower in fat.

A physician prescribing any drug for weight loss should also be simultaneously prescribing lifestyle changes. No drug can substitute for these important lifestyle changes, and all drugs on the market are effective only when coupled with those changes.

Shape Up America will continue to educate physicians and consumers alike about the appropriate use of pharmacotherapy. Specifically that means a continued emphasis on healthy eating and increased physical activity because our goal is to see all

Americans achieve and maintain a healthier body weight and not just a lower body weight.

I thank you for this opportunity to share my views with the Committee.

CHAIRMAN BONE: Thank you very much.

The next speaker is Dr. James Anderson from the University of Kentucky Medical School in Lexington VAMC.

DR. ANDERSON: Thank you.

I'm Dr. Jim Anderson, Professor of Medicine and Clinical Nutrition at the University of Kentucky. You should have a copy of my presentation. Unfortunately that does not reflect my -- I've served as a consultant for Hoffman-LaRoche and received research grants from them.

I direct the University of Kentucky weight management program, and over the last 30 years our research group has published 250 peer reviewed papers and book chapters in books, many of which are related to obesity.

I also coordinate the Obesity Research Network, which is a group of 18 academicians and clinical investigators, including Dr. Dick Atkinson, Jim Hill, Frank Greenway, Xavier Pennier (phonetic), Tom Waddon (phonetic), and Rena Wing, who do clinical

trials in obesity and consult with companies about design.

Recently this group had a consensus conference, and this report on clinical trial design for obesity agents will be published in Obesity Research.

Since 1974, our research group has been active in developing nutrition therapy for diabetes, obesity and dyslipedemia. Since 1985, I've directed an intensive weight management program using behavioral treatment, and we've treated over 3,000 people with obesity. We have an effective program. The average person who enrolls and who attends our first class loses 25 kilograms over 22 weeks.

Our long term success has been recently evaluated, and at five years our people are keeping off 23 percent of the weight they lost on average. If you look at success defined as keeping off ten percent of their initial weight, 25 percent of our people are keeping off ten percent of their body weight at five years and 40 percent are keeping off five percent or six kilograms at five years.

So I think it's clear that we can help people lose weight, but maintaining weight is suboptimal. Over the last three years we've been

involved in clinical research looking at adjunctive drug therapy. We've examined the question of whether adjunctive use of drugs helps us be more effective in our treatment.

Our experience indicates that adjunctive drug treatment helps people lose more weight and stay in their program longer. In one uncontrolled clinical trial where we provided adjunctive drug therapy over 15 weeks, people lost two kilograms or significantly more than historical controls.

We've also examined the effect of adjunctive drug therapy and weight maintenance over the first year, and those persons on phentermine, the agent we used, were able to maintain their weight for the 16 week segment very well, whereas persons who were not on adjunctive drug therapy gained the expected 5.6 kilograms. These differences were statistically significant.

Our experience indicates and the literature indicates that adjunctive drug therapy helps people lose more weight and lower the risk factors more effectively. Adjunctive drug therapy also helps people maintain their weight loss better.

We need a variety of obesity agents that can be tailored to the needs of the individual person.

We've had some clinical experience with orlistat. We treated 53 people with orlistat for a year as a part of a multi-center, double blind study. Our experience was that people receiving orlistat maintained their weight much more effectively over the year than we would expect from our experience.

Data from the entire trial indicated that persons with placebo gained as you would expect about 59 percent of their weight loss in the first year. Persons on orlistat treatment, 120 milligrams per day t.i.d., gained only 30 percent of their initial weight loss.

In our experience, orlistat was well -- yes -- was well tolerated by people and most wanted to continue the drug.

I think orlistat has distinct advantages in the treatment of obesity because it doesn't have CNS or cardiovascular side effects.

This agent was well tolerated by our patients and I think will be useful for selected individuals. Based on my own experience and review of the literature, I recommend approval of orlistat.

Thank you.

CHAIRMAN BONE: Thank you very much, sir.

The next speaker is Eric or -- excuse me.

Is there a representative here from the United Seniors Health Cooperative?

If not, Ms. Reedy will read a letter from Eric Shulman.

MS. REEDY: "United Seniors Health Cooperative is concerned about the possible link between the use of Xenical and breast cancer. We, therefore, request that the Food and Drug Administration and its Endocrinologic and Metabolic Drugs Advisory Committee carefully consider this issues before approving Xenical for use in the treatment of obesity.

"USHC is concerned about the fact that other diet drugs have been approved by FDA that subsequently demonstrated serious health consequences. In our view, older people should adopt proper exercise and dietary standards to control weight, but we also believe FDA must proceed very cautiously in bringing new diet drugs to market such as Xenical.

"Data from the Centers for Disease Control show that over 40 percent of seniors between the age of 55 and 74 are overweight. This compared to a 33 percent overall rate. In particular, the CDC data shows that from 1988 to 1991, 48.7 percent of females aged 55 to 64 were overweight. Since these seniors

represent the largest by percentage groups of overweight persons in the United States, it is quite reasonable to assume that they will be among the highest percentage users of weight control drugs. This fact is confirmed by the results included in FDA's July 8th, 1997, public health advisory on phen-phen and the CDC's report on cardiac valvulopathy associated with phen-phen in the November 14th, 1997, issue of Morbidity and Mortality Weekly Report.

"We are concerned that even a small increase in the risk of breast cancer due to the use of Xenical could have a serious impact upon this group of women. If a substantial number of them began to use the drug and if a linkage between the drug and breast cancer exists, the number of women adversely affected could be significant.

"We understand that the health risks associated with obesity, such as increased incidence of diabetes, hypertension, and stroke, are serious and that treatment of this condition should be a high priority. However, we feel that there is no need to rush into the approval of Xenical. Important questions about safety must be thoroughly and carefully reviewed to minimize increased risk to this population. This is especially true because other

drugs and therapies for the treatment of obesity are already available.

"United Seniors Health Cooperative is a nonprofit organization comprised of thousands of consumers, advocates, and elder care professionals throughout the country. As a leading advocacy group for senior citizens in the United States, we are concerned with issues that have significant impact on seniors' health. Breast and obesity are issues of genuine concern to our members.

"Recently published reports about the linkage between Xenical and breast cancer have come to our attention, and we urge the FDA to proceed cautiously, reviewing all of the data carefully, before approving this diet drug.

"Sincerely Eric Shulman, president and CEO."

CHAIRMAN BONE: Thank you, Ms. Reedy.

The next presentation will be by David Allison from the North American Association for the Study of Obesity.

MR. ALLISON: Good morning.

I'd like to thank the Committee for this opportunity to share some thoughts with you. My name is David Allison, obesity researchers at Columbia

University and a council member of the North American Association for the Study of Obesity, or NAASO.

I've been asked on behalf of NAASO to make a statement today, and let me point out by way of disclosure that in the past I've organized two conferences both of which were contributed to financially by a number of pharmaceutical companies, including Hoffman-LaRoche.

Obesity is a major public health problem in the United States. Because of its high prevalence and causal relationship with many serious medical complications, including diabetes, hypertension, dyslipedemia, heart disease, cancer, gastrointestinal disease, lung diseases, arthritis, sleep disorders, and premature death.

The prevalence of obesity has markedly increased in the past 15 years in almost all industrialized countries in the world. Data from the third national health and nutrition examination survey and HANES III demonstrate that currently 54 percent of adults are obese or -- excuse me -- overweight as defined by a body mass index of greater than 25 kilograms per meter squared and approximately 25 percent of children and adolescents in the United States are overweight.

The cornerstone of obesity therapy involves the difficult process of implementing lifelong lifestyle modifications in dietary intake and physical activity.

Pharmacotherapy can be used as an additional tool to help some patients achieve successful long term weight management. It is hoped that the development of effective and safe pharmacologic agents for the treatment of obesity will continue as we increase our understanding of the mechanisms that regulate energy balance.

The North American Association for the Study of Obesity, NAASO, recommends that pharmacotherapy only be used for obese patients and as part of a comprehensive weight management program, which includes a medical examination, diet counseling, physical activity education, and behavior modification.

It is unlikely that most obese patients can achieve an ideal body weight with current treatment options. However, loss of as little as five to ten percent of initial weight improves several of the medical abnormalities associated with obesity, including glucose intolerance, high blood pressure, and dyslipedemias. Therefore, a modest amount of

weight loss, as long as it is maintained, can have considerable clinical benefits and is a realistic goal for many patients.

When properly used, pharmacotherapy can help selected patients achieve these long term weight management goals. It is important that effective and safe therapies continue to be developed to help millions of Americans suffering from medically significant obesity.

At the same time it is critical that we increase our efforts to develop and implement successful public health policies to help prevent the onset of obesity, particularly in young children and adolescents.

the North American Association for the Study of Obesity is an interdisciplinary scientific society whose purpose is to develop, extend, and disseminate knowledge in the field of obesity.

Thank you.

CHAIRMAN BONE: Thank you very much.

The next presentation is from Dr. Priscilla Hollander of Baylor University.

DR. HOLLANDER: Thank you, and my name is Dr. Priscilla Hollander, and I'm Director of the Diabetes Center at Baylor University Medical Center in

Dallas.

I participated as a clinical investigator in the study of orlistat in Type 2 diabetes, and so I appreciate the opportunity to be able to speak to the Committee and the group here today in regards to what I think is the importance of a pharmacological therapy like orlistat in the treatment of patients with this syndrome.

I think we all know that about 15 million people in the United States have diabetes, and we, again, I think are all familiar with the morbidity and mortality associated with disease, and so I will not go into details in terms of those statistics.

I think the important thing is in regard to the link between obesity and Type 2 diabetes, and roughly 80 percent of all patients with Type 2 diabetes are obese.

I think if we can break the cycle of obesity, we can also help break the cycle of diabetes both in patients who actually are already diagnosed, and I think there is great potential for looking at a weight loss drug in regard to prevention of diabetes.

I think this is especially important in light of the fact that we now have new diagnostic criteria for diabetes, and so that we actually are

recognizing this disease in its earlier stage.

Recently I had the opportunity to participate in a national teleconference beamed to a number of cities around the United States. This was sponsored by the University of Minnesota and by the American Diabetes Association, and I think the focus of this conference actually was to spread the news, I think, to primary care physicians, internists, health professionals, people who were interested in diabetes about this link between obesity and diabetes, and I think the response really was tremendous.

Obviously there is a large audience out there. We are looking for new approaches to obesity. So I'm really going to make this very short, and I think historically and unfortunately we've had little success with diet, exercise, and behavioral therapy. Not to say that they're not important, but a recent study, I think, reported by Rena Wing in Diabetes Care, again, emphasized the sort of pessimistic sort of outcomes that we see using this approach, and this was in patients with diabetes.

And so basically I think if we can add a safe and effective pharmacotherapy to our sort of armamentarium of treating obesity, I think we will be very far ahead, and I think one of the other important

facts in this regard and which has impressed me about this drug is the ability for long term maintenance.

And so with that I thank you.

CHAIRMAN BONE: Thank you, Dr. Hollander.

This concludes the open public session of the or section -- I'm sorry -- of the meeting. We'll proceed to the presentations by the sponsor and the Food and Drug Administration.

And I should just explain just for a moment that there will be a presentation by the sponsor, followed by an FDA presentation, and then we will have an intermission, and then there will be another presentation by the sponsor specifically addressing the breast cancer issue, and a further presentation by the FDA specifically addressing the breast cancer issue.

So we're going to have sort of general presentations looking at the big picture, everything except breast cancer, and then come back to focus on that very important issue separately.

The Committee members are invited to ask for points of clarification after each of the individual speakers, but to reserve discussion or more general questions until the appropriate time in the afternoon, and if we're able to stay with the

schedule, we will have the entire afternoon for that kind of questions and discussion. So I think this will be very useful for all of us.

How will the Hoffman-LaRoche speakers be introduced? Is there someone introducing for all of you? Yeah, all right.

We'll now begin the section of the program devoted to the sponsor's general presentation.

MR. LUCEK: Good morning, Dr. Bone, Dr. Sobel, members of the Advisory Committee, ladies and gentlemen, invited consultants.

I am Rudolph Lucek, Group Director in the Department of Drug Regulatory Affairs. I'd like to thank the members of the Committee for their time in preparing today's meeting. I'd like to thank the members of the Metabolic and Endocrine and Oncology Division for their time and effort in the review of this application.

Xenical is the proprietary name for orlistat, a selective and slowly reversible inhibitor of gastric and pancreatic lipase. Orlistat is the first of a new class of anti-obesity agents having a novel site of action, its activity being localized in the gastrointestinal tract. Orlistat also has a unique mode of activity in that it reduces the

absorption of some ingested fat.

An NDA for the use of orlistat for the treatment of obesity and long term weight management was filed with the Food and Drug Administration in November of 1996. this application was granted priority review and presented before the Metabolic and Endocrine Advisory Committee in May of 1997.

This resulted in a unanimous vote of eight to zero for approval. At that advisory meeting information concerning the incidence of breast cancer observed in the Phase 3 clinical studies was reported. While this incidence was low, there was an imbalance in the distribution of these cases, a greater proportion of the cases occurring on patients treated with orlistat than on placebo. Therefore, all data available at the time was analyzed and reviewed by a panel of experts, which resulted in the following opinion which was presented to the Advisory Committee in May of 1997 and which was consistent with the review presented by the FDA on this issue.

Mutagenicity, genotoxicity, and carcinogenicity studies in animals with systemic exposures to many multiples of that in man showed n o evidence that treatment with orlistat had any carcinogenic potential.

Times to diagnoses of a number of the breast cancer cases were too soon after randomization for the case to be due to treatment. The direct causative effect of orlistat is unlikely due to its negligible systemic absorption.

There was no mechanism resulting from a secondary effect of orlistat that could be identified linking orlistat to breast cancer, and it was, therefore, concluded that chance or detection bias were possible explanations for the observed imbalance.

During the Advisory Committee meeting, the Committee requested additional information concerning the observed cases of breast cancer.

To further investigate if there was any relationship between orlistat and the occurrence of breast cancer and following extensive discussions and in collaboration with the FDA, a multidisciplined analysis of the breast cancer cases was undertaken. All data concerning the reported cases of breast cancer were collected, including patient medical records, pre and post study mammograms, and histopathology slides.

An extensive investigation was undertaken which included a follow-up survey of all female patients 45 years old and older who participated in

the Phase III clinical studies. A complete review of each breast cancer case was conducted by independent experts in the fields of epidemiology, radiology, oncology, and pathology. In all, we consulted over 30 experts during this evaluation.

In addition, all histopathology slides were given to the Armed Forces Institute of Pathology for independent evaluation. Today we will be presenting the results of this battery of in depth analyses.

However, for members of the Metabolic and Endocrine Committee who were either new to the Committee or were not present at the previous orlistat advisory presentation and for the assistance of invited expert consultants joining us today, we will begin with a review of efficacy and tolerability of orlistat, demonstrating that orlistat is both well tolerated and associated with significant and sustained weight reduction and an improvement in co-morbidity risk factors in patients who are clinically obese.

This presentation will begin with a brief summary of obesity as a risk factor for co-morbid conditions given by Dr. Aram Chobanian And Dr. Douglas Greene. Dr. Jonathan Hauptman will then present

efficacy and tolerability, and Dr. Eric Colman will present for the FDA.

For a detailed presentation of efficacy and tolerability we refer the Committee to the briefing document provided prior to today's meeting.

We will then turn our attention to a discussion of the breast cancer cases observed in the Phase 3 clinical studies. A review of the observed breast cancer cases and an analysis of possible biological mechanisms will be presented by Dr. Martin Huber and Dr. Timothy Anderson from Hoffman-LaRoche.

Additionally, they will be joined by Dr. James Schlesselman and Dr. James McGee. Dr. Jonathan Hauptman will then conclude with a benefit-risk assessment. Presenting the FDA's review will be Dr. Bruce Stadel and Dr. Eric Colman.

Due to the specialized nature of some of the areas to be discussed today, we are also accompanied by a number of consultants. I would also like to mention that none of the consultants with us today or any of the experts who contributed to the evaluation of the data before you have any financial interest in Hoffman-LaRoche or in orlistat. These consultants are available to assist in addressing Committee questions and may be called upon by

presenters to add comment and clarification.

A consultant list, including CVs has been provided to the Committee. They are Dr. Gary Williams, Dr. Andrew Seidman, Dr. Stephen Feig, Dr. Bess Dawson-Hughes, Dr. James Olson, Dr. Dennis Ahnen, Dr. Michael Wargovich, Dr. Michael Jensen, and Dr. David Kelley.

I would now like to turn the meeting over to Dr. Chobanian, who will begin with a brief summary of obesity as a risk factor for co-morbid conditions.

DR. CHOBANIAN: Thank you, Dr. Bone, Dr. Sobel, members of the panel, ladies and gentlemen.

I've been asked to speak about the effects of obesity on cardiovascular risk and cardiovascular disease in the U.S. population. We've already heard about prevalence data in the United States with respect to obesity. Shown here are data in women taken from the NHANES study.

As we have heard, overall about 30 percent of adult women in the United States have obesity as defined in a BMI, a body mass index, of greater than 27, and about ten percent could be considered as very obese with body mass index of greater than 32.

The numbers increase in age up until about age 64, with some decrease thereafter. The data in

men follow the same pattern, though are somewhat lower.

Life insurance statistics and other data demonstrate clearly that excess weight is associated with increased mortality. Plotted on this slide are BMIs versus mortality ratios. As can be seen, there's a curvilinear relationship with increased risk of death from BMI levels of about 25 upward.

A variety of iterations of such data have been provided from other studies. In general, in those with body weights 20 percent above average, excess mortality averages 20 percent higher in men and ten percent in women.

No carefully controlled, large trials have been performed to determine whether decreasing body weight in the obese will improve longevity, but considerable data are available relating to risk for cardiovascular disease, and I will deal with those in my presentation.

Obesity represents an independent risk factor for cardiovascular disease. However, more importantly, it also is associated with adverse changes in several other risk factors. One of these is high blood pressure.

As shown in these data taken from the

NHANES 3 survey, the prevalence of high blood pressure increases considerably at BMI levels of 25 or greater, with more than doubling of overall prevalence with the highest levels of BMI.

In absolute numbers, a ten kilogram higher body weight would be associated with about a five over three millimeter higher average blood pressure level and a 15 percent increase in overall cardiovascular disease risk.

The NIH's joint national committees and several other groups have long recommended weight reductions as an integral component of the management of high blood pressure. Most hypertensives have a lowering of blood pressure with weight reduction even if the decrease average is only five to ten percent of body weight.

Unfortunately recidivism, as you know, is a major problem in hypertensive, as well as normotensive obese individuals.

A number of studies, including the trial of hypertension prevention, have shown that reducing body weight in the obese is important in preventing the development of high blood pressure. In studies that have been carried out with references shown here, subjects with high normal blood pressures, defined by

130 over 39 systolic and 85 to 89 diastolic, were followed over a period of time. A three to four kilogram decrease in both weight was associated with a two to three millimeter of mercury decrease in systolic and diastolic blood pressure, and remarkably, in this high normal group, there was a 50 percent lower incidence of hypertension developing over a three to five year period.

These data have now been confirmed in several clinical trials.

Serum lipids and lipoprotein protein abnormalities are also associated with excess body weight. As noted, the presence of hypercholesterolemia, as defined by total cholesterol levels of 240 or greater, increases substantially in men with BMIs exceeding 27 and in women with BMIs exceeding 25. Again, these are data from the NHANES study.

The increase in prevalence averages about 50 percent at the highest levels of BMIs.

Similar findings are observed when we look at low HDL cholesterol levels and their prevalence. The low HDL here is defined as 35 or less in men and 45 or less in women.

With BMIs of 25 or greater, there is a

more than doubling of the presence of abnormally low HEL levels with a prevalence of as much as 42 percent in women.

Modest changes in body weight of five to ten percent are associated, in general, with a five to ten percent decrease in plasma cholesterol, or that translates into a ten to 20 milligram per deciliter change. This may not seem like much, but if we look at data from cholesterol intervention studies prior to the use of the statim type drugs, such changes would still appear to be meaningful.

For example, in the lipid research clinic study which used a combination of diet and resins, for every one percent decrease in total cholesterol there was a two percent reduction in coronary risk. In other studies of shorter duration, less than four years' duration, a one milligram per deciliter change is associated in those studies' meta analysis with about a one percent change.

Risk factors tend to cluster, particularly in obese individuals. In this slide, data are shown for four different risk factors in individuals that are considered lean in Framingham, with BMIs in the lowest quintile of less than 22, and individuals who are obese with BMIs of greater than 27.

As you can see, in both men and women -- there's an error here. It should read 125 -- that the obese individuals have increases in systolic blood pressure, diastolic blood pressure, total cholesterol, total glucose.

Dr. Greene later will talk about glucose and diabetes control as they relate to risk factors, and I'm not going to touch on that.

But as you can see, the obese individuals have very substantially higher levels of blood pressure, about ten millimeters of mercury, systolic blood pressure, similar amount with diastolic blood pressure, with cholesterol levels somewhere between ten and 20 milligrams per deciliter.

A large fraction of individuals who develop coronary disease have two or more abnormal risk factors. In the Framingham data set, 55 percent of CHD events in men and 78 percent in women occurred in individuals with two or more risk factor abnormalities.

The overall impact on the sum total of abnormal risk factors is favorably affected by weight reduction and adversely influenced by weight gain. Depicted here are the relative changes in the overall sum of risk factors in those who lost or gained

weight.

In both men, shown on the left, and women, shown on the right, weight loss of greater than five pounds was associated with about a 50 percent decrease in the risk factor sum, whereas weight increase of greater than five pounds caused a 20 percent increase in sum in men and about a 40 percent increase in women.

These studies were carried out over a 16 year period. Unfortunately, only seven percent of the obese men and six percent of the obese women lost more than five pounds over the 16 year period.

In conclusion, obesity has an important effect on cardiovascular risk and cardiovascular disease and increases the degree of clustering of risk factors. Weight reduction can favorably affect cardiovascular risk by influencing several risk factors simultaneously.

I'd now like to introduce Dr. David Greene, who will continue the discussions and concentrate on diabetes and glucose control and risk.

Thank you.

DR. GREENE: Thank you, Dr. Bone, Dr. Sobel, members of the panel and FDA, ladies and gentlemen.

I'm here to deliver a very simple message, which has actually already been well covered by the public speakers this morning. So I'll be quite brief.

The basic message is that weight management is a vital and missing element in the control of Type 2 diabetes.

Diabetes is a disease which greatly exceeds just the problem of hyperglycemia. It really is a disease of multiple risk factors and multiple risk factor management, as is illustrated in this slide from the MRFIT study showing cardiovascular death in patients who have diabetes in the hatched bars and people who don't as a function of risk factors, other risk factors than diabetes, and as you can see, there's a great excess cardiovascular mortality in people who have diabetes independent of other risk factors.

And so the overall problem in the management of Type 2 diabetes is an issue of management of overall risks, including not only glycemic control, but other cardiovascular risk factors, including hypertension and dyslipedemia, and then the issue is that when we try to manage one, sometimes we lose control of the others.

The treatment of Type 2 diabetes has

dramatically improved, in part, as a result of the actions taken by this Committee over the last few years, in addition to diet and exercise, which is the mainstay of anti-diabetic therapy. Pharmacotherapy has greatly expanded with the introduction of biguanides, a new drug to us, an old drug to the rest of the world, and various other agents which are very useful in the control of hyperglycemia.

Unfortunately, the use of this armamentarium even in the best of hands is associated with adverse events of therapy. This is a slide taken from the United Kingdom prospective diabetes study, probably the most extensive and well supported, long term clinical trial in Type 2 diabetes, and if we look at patients who were randomly assigned to either continued diet therapy, metformin, or intensive therapy with insulin plus sulfonylureas, we can see that there's an initial fall in hemoglobin A1c, an initial fall in fasting plasma glucose, but that this is subsequently followed by a creep of loss of metabolic control, which at least in the patients assigned to intensive anti-hyperglycemic therapy is associated with a progressive increase in weight, despite active and intensive lifestyle modifications as part of this clinical trial.

These are patients who had mild to moderate hyperglycemia upon entry into the study, between six and 15 millimolar fasting plasma glucose after initiation of diet therapy.

If we look at the U.K. PDS data which has been published very recently, looking at those patients with more severe diabetes, those whose fasting plasma glucose was 15 millimolar after initiation of diet therapy, we can see a similar trend. These patients are divided between non-obese and obese patients, and these patients were assigned to either insulin, sulfonylurea or metformin, and you see similar trends, an initial fall in hemoglobin A1c, followed by a slow creep, which is associated with weight gain in the intensively treated insulin and sulfonylurea patients, somewhat less weight gain in the metformin group, but again, the same trend.

And so if we summarize the U.K. PDS data, we see progressive worsening of glycemia after initial introduction of therapy associated in some groups with progressive weight gain, and the potential for exacerbation of cardiovascular disease risk.

And so what we would like to see added to this armamentarium of diet, exercise, pharmacotherapy would be additional measures of weight management.

The ideal characteristics for a weight management component to the treatment of Type 2 diabetes would be therapy that would potentiate initial weight loss, prevent weight gain, have beneficial effects on glycemic control, improve co-morbidities, and potentially would spare the use of some hyperglycemic agents which may have adverse effects, including weight gain.

If we look at the ability of lifestyle changes to accomplish this, even in the very best hands, we find that this is a difficult and frustrating endeavor. This is a slide of data recently published by Rena Wing looking at lifestyle change in patients who don't have diabetes, but who have first degree relatives with diabetes over an extended period of treatment.

And what you can see is in the patients that were randomly assigned to either diet alone or diet plus exercise, there's an initial fall in body weight, which over the subsequent two years is essentially lost, and if we look at co-morbidities, LDL, cholesterol, triglyceride, there's really very little effect in lifestyle management even in the best of hands in a very active behavior modification program.

So we clearly would like to have something more than just lifestyle changes. What kind of desired characteristics would we have for a safe and effective pharmacotherapy to use as an adjunct to the treatment of Type 2 diabetes? It would be something that potentiates weight loss, minimizes or prevents regain, achieves clinically significant weight loss that is associated with health benefits, and what would be ideal would be an adjunctive management program that also were possibly to prevent diabetes in obese people who are at high risk.

So the bottom line is that there is a missing element to our armamentarium of anti-diabetic treatment, and that is something to help us manage the weight gain problem which is associated with the disease itself and with its treatment.

Thank you very much.

DR. HAUPTMAN: My name is John Hauptman, and I work in the Clinical Research Department at Hoffman-LaRoche.

Orlistat is a drug to be used as an adjunct to diet by people with medically significant obesity who need assistance in achieving a weight loss, that is, patients with a body mass index of at least 30, which is equivalent to being 30 percent

above idea body weight, or in the presence of risk factors such as Type 2 diabetes, impaired glucose tolerance, hyperlipidemia, or hypertension, a body mass index of at least 27.

Orlistat is unique as a treatment for obesity for several reasons. Unlike all of the other available agents, orlistat is it no an anorectic. It does not act in the central nervous system, and it does not require systemic absorption for its effect.

Since obesity is due to an excess intake of calories, which many people believe comes largely from fat, it would seem reasonable to selectively inhibit calories from fat rather than those calories from proteins or carbohydrates. Orlistat acts locally within the lumen of the gastrointestinal tract where it inhibits pancreatic and gastric lipases.

Fat in the form of triglycerides cannot be absorbed without first being hydrolyzed by these lipases in the free fatty acid and monoglycerides. The free fatty acids and monoglycerides are transferred into colonic mucosal cells, repackaged, and then enter the systemic circulation by the lymphatics.

Orlistat then binds to pancreatic and gastric lipase, rendering much of it inactive. At the

clinical usage dose, approximately 30 percent of ingested fat, or about 20 grams per day, is not broken down and, therefore, left intact within the intestine to pass out of the body unabsorbed.

The calories in the fat are no longer available as an energy source, and additional weight is lost by producing a constant caloric deficit above and beyond that which can be achieved by dietary change alone.

Now I would like to review some of the key efficacy and safety data presented to this committee last May.

Since obesity is a chronic disease, the emphasis of our program was long term treatment. The majority of the Phase 3 studies were two years in duration. Up until now, this has not been done on any systematic basis for weight loss drugs. Although the FDA criteria for evaluating weight loss drugs did not become public until 1995, the design of our program, which predates that, meets these criteria.

The program is designed not only to evaluate the effect on weight loss, but also the effect and characterize the effect in obesity related risk factors.

We conducted seven Phase 3 clinical

studies in over 4,000 patients. Five of those studies evaluated weight loss and maintenance for one year. Four of those studies went on to have a second year of double blind placebo treatment.

We did a special study in patients with Type 2 diabetes who were obese and were maintained on oral hyperglycemics, and we did a separate study evaluating only the prevention of weight regain after weight loss occurred with the diet.

The studies consistently showed that as part of an overall weight management program, orlistat helps to produce a long term, clinically meaningful weight loss. Our studies also demonstrate favorable effects on risk factors associated with obesity.

Our goal in the first year of the studies was to produce and then maintain a weight loss. All patients received the high standard of care as we know it today which included behavioral counseling, dietary counseling, a balanced hypocaloric diet.

Based on this, the placebo treated group was actually an active comparator. The studies were designed to test and quantify the additional effect of orlistat on an effective weight loss regimen.

Now, we know that as hard as it is to lose weight, the natural tendency is to regain it. The

purpose of the second year of our studies was to try to evaluate if orlistat could, in fact, help decrease the weight regain that naturally occurs.

In order to do that, the studies had to be designed in a way to insure that some weight gain would occur to test the effect of the drug. The goal in that second year was not to maintain the loss, but to test whether or not we could prevent any of the regain.

Diet was reevaluated to meet the needs of the patient's new body weight at the end of the first year. If a patient was still losing weight, his diet was increased. Counseling and clinic visits changed. The counseling was no longer to lose weight, but to try to maintain what they could. The clinic visits were up to two months apart, which is typical of what an out-patient treatment program might be.

If a patient began to gain weight during year two going back on a hypocaloric diet was not allowed. Rather, the patient was encouraged to maintain whatever weight they were at that time.

Due to the limits of time today I'll present data from one of our two year studies that looks at all major aspects of weight control, including weight loss, weight maintenance, and

prevention of weight regain. Nevertheless, all of the studies that we've done are consistent, and for details, I refer you to our briefing document.

The second part of my talk will deal with the effect of orlistat on obesity related risk factors.

Study BM1419C was a large, multi-centered, double blind study. After patients were screened, they entered into a placebo lead-in period which was given with a diet, a hypocaloric diet. At the end of four weeks, regardless if the patients were losing weight or not, they were then randomized to continue on to placebo or 120 milligrams of orlistat three times a day for one full year in association with the weight loss diet.

Please note and remember at the end of the first year several things changed. The diet was now called a eucaloric diet, and it was designed to meet their new dietary needs of their lower body weight.

Also, patients in the placebo group were randomize reassigned to other placebo or 120 in the second year or those patients on orlistat were rerandomized to look for the effect in this group.

This was a large study, over 680 patients, and please note that the mean BMI was 36. So this is

a population of patients who had significant degrees of obesity.

What we have here is the mean weight loss over time. Knowing that the average body weight of patients in this study was 100 kilograms will help as we go through the data.

During the four week lead-in period patients lost in both groups approximately two and a half to three percent of their body weight. After randomization, those patients on placebo continued to lose weight until about week 24 and then had a plateau. So by the end of one year, they lost about six percent of their body weight or about six kilograms.

Those patients on orlistat 120 had a rapid separation in their effect from the placebo group. Weight loss continued down to week 34 and then plateaued and maintained itself. At that time there was a ten percent decrease in body weight, which is approximately ten kilograms.

We believe that this is a very rigorous test of the effect of orlistat, as can be seen by the fact that the placebo group, in fact, lost a significant amount of weight.

Statistical significance was tested using

the least square means differences between the orlistat and the placebo group from randomization until the end of treatment based on the last observation carry forward technique. The differences here are highly significant. It was P less than .001.

Those patients on orlistat lost an additional 70 percent greater weight than those patients on placebo.

The key parameter that the agency uses to evaluate if a drug is effective for weight loss is looking at the percentage of patients in each treatment group that loses at least five percent of their baseline body weight. From the study that we just saw, those patients on placebo who lost more than five percent of their body weight was about 27 percent of the patients. Fifty-five percent of the orlistat patients lost at least five percent.

If you go to the more rigorous criteria of losing at least ten percent of their baseline body weight, not taking into account any of the weight that occurred during the lead-in period, 25 percent of the orlistat were to lose at least ten percent compared to eight percent on placebo, and again, these differences were important.

Looking at the prevention of weight

regain, as I mentioned before, first we'll look at those patients on placebo. During the first year they lost approximately six percent of their body weight. At the time of rerandomization, the patients who continued on placebo regained about two and a half kilograms while those patients who were on orlistat not only did not regain, but continued to lose an additional kilogram.

The patients on placebo regained 43 percent of what they had lost the year before compared to patients on orlistat losing an additional 15 percent.

Looking at those patients on orlistat the first year who lost approximately ten percent of their body weight, rerandomization to placebo produced an increase of 5.6 kilograms. Those patients who continued on the drug, on orlistat, regained about two and a half kilograms, and please remember that this part of the study was not designed to keep all of their weight off. It was designed to look for the ability to help prevent the regain that naturally occurs. These differences were highly significant.

The patients on placebo, as seen in white, regained on average 52 percent of the weight they had lost compared to those patients on orlistat who only

regained 26 percent, and a large percent of those patients regained no weight at all.

Then finally, looking at those patients who had orlistat for two full years compared to placebo for two full years, we see the following. The key point here is despite the fact that there was some regain in the second year for both treatment groups, the effect of orlistat was maintained as shown by the fact that the differences between treatments was similar at the end of two years as compared to the end of one year, and again, at the end of two full years of treatment, those patients on placebo lost approximately 4.6 percent of their initial body weight, while those patients on orlistat lost close to eight percent of their body weight.

The consistency of the results can be seen across studies. These data represent the effect seen after the first year of all of our two year studies. Each of these studies contain between 600 and 900 patients.

Based on the FDA criteria of a greater percentage of patients on drug losing at least five percent of the baseline body weight, these studies confirm the efficacy of orlistat, and if you agree that medical benefits begin at the five percent weight

loss level, then the additional weight loss effect of orlistat puts more patients into the weight loss category of five percent than does the placebo group.

Looking again at the more rigorous criteria of ten percent at the end of one year, we see the exact same consistent effect, and I'd like to draw your attention all the way to the right of the slide. You can't see it, but it's Study 14161. I think somebody might have to duck down.

What that shows is that those patients -- this study was important because it was done only by primary care providers. These were physicians who are not experienced in the treatment of obesity or even diabetes.

What we saw in this study was that 20 percent of the orlistat patients were able to keep off at least ten percent of their body weight compared to only four percent of the placebo patients in the group of doctors who treat primary care patients.

And now looking at two full years of data, although there are no guidance criteria for what to find at two full years, we see here that the effect is absolutely consistent, that the differences that we saw at the end of one year with the ten percent weight loss criteria is the same as we see at the end of two

years for the weight loss criteria, and again, in the study all the way to the right of the slide, we see exactly the same effect for those patients in this primary care study.

Although weight loss by itself is an important goal, it might be even more important to look at obesity related risk factors since that is the source of much of the increased morbidity and mortality. The studies were designed to look at risk factors in both the entire study population, as well as those patients who were abnormal at baseline.

For today's purposes, I will limit the presentation to those patients with abnormal values prior to treatment. To be able to analyze this important group of patients, we did a meta analysis using the integrated database in the first year of study since the designs of those studies were similar and allowed us to do this.

Nevertheless, results from individual studies are consistent and support the conclusions from the integrated analysis. For each of these key areas that you see here, there are overall improvements in the orlistat group, and these improvements were almost always significantly greater than the placebo group.

First I'll go through some of the cardiovascular risk factors. For those patients who, after four weeks of already being on a diet still had an LCL cholesterol level greater than 3.36 millimoles per liter, which is 130 milligrams per deciliter, there was a small decrease during the first four week lead-in period, but after randomization, those patients on placebo had no additional benefits even though they continued to lose weight.

Those patients on orlistat lost an additional eight percent and maintained that effect over the entire period of time.

Now, there's another way of showing this effect, and that's to evaluate patients who are abnormal at baseline and evaluate whether or not they were able to normalize at the end of treatment.

What we see on this slide is that of the 516 patients in our study who have abnormal elevated LDLs and were on placebo, 14 percent became normal at the end of the study. Of the 660 patients on orlistat who were abnormal, close to 32 percent of those patients normalized by the end of treatment.

And then to show the effects maintained over two years, we look at the entire effect of the treatment from initial, looking at the differences

between the orlistat group and the placebo group, and this effect was maintained.

Next we'll look at the LDL/HDL ratio. Those patients on placebo and orlistat both had decreases over time associated with their weight loss, but the effect of the orlistat group was about a 50 percent greater lowering of the LDL/HDL ratio, and these differences were significant, and again, these differences were maintained over the two years of treatment.

Weight loss, as we know, is important in the treatment of hypertension. These are patients who had elevated blood pressures after already being on the treatment, on weight loss for four weeks. During the first 12 or 16 weeks of weight loss treatment, both groups had a decrease in their diastolic blood pressure. Then those patients on placebo plateaued out and increased a little bit by the end of the study. So at the end of treatment, they had a 5.5 millimeter of mercury decrease in their blood pressure.

Orlistat patients lost greater and continued to lose a small amount so that by the end of the study the decrease from the time of randomization was about eight millimeters of mercury, and again,

these differences, which are probably made up by the difference of weight loss in the orlistat patients compared to the placebo, were greater than the placebo group and were maintained over the two years.

We wanted to look at the overall effect of orlistat on carbohydrate metabolism. Let's take a look first at what happens to those patients with fasting insulin levels in the top quartile or greater.

During one year of treatment both the placebo patients and the orlistat patients did have a decrease, and that decrease at least in this instance was actually even greater during the second year of treatment.

We did oral glucose tolerance testing in over 1,000 patients in our program. We saw significant decreases in glucose, insulin, and C peptide measures as looked at under areas under the curve.

Now, to show the clinical benefit of these results, we looked at a shift table of carbohydrate metabolism in patients with impaired glucose intolerance. What's very important about this slide is those patients with impaired glucose tolerance have the opportunity to improve to normal or worsen, to become diabetic.

Of the 48 patients who were on the placebo group, 45.8 percent of them became normal based on an OGTT, and 10.4 percent of those patients worsened to become diabetic. Of the 115 patients with impaired glucose tolerance at the end of the first year on orlistat, 72.2 percent of those patients now had an absolutely normal oral glucose tolerance test, and only 2.6 percent of those patients went on to develop diabetes.

The effects were maintained during the second year as well, although the numbers are slightly smaller. This looks at those patients who had a value at baseline and then two years later, and, again, we see that the effects of orlistat on oral glucose tolerance testing in these patients was absolutely maintained with fewer people developing diabetes and a greater percentage of people having now normalized abnormal glucose tolerance tests.

Before there was mention of a study that was done only in patients with Type 2 diabetes who were obese and were on oral sulfonylurea medications. This study had a five week lead-in period with patients on a diet that then were randomized to orlistat or placebo. The first goal of that study was to look at body weight change, and we know that this

population of patients is very resistant to weight lost because they're on sulfonylureas.

During this study the placebo patients lost after a year about four percent of their initial body weight. Those patients on orlistat lost about six percent of their initial body weight, and these differences were significant statistically and clinically, and I'll show you next what the value of this additional weight loss was.

We looked at the need for sulfonylurea treatment. Medication withdrawn means that the patient was no longer requiring oral diabetic medication to control their diabetes. The same goes for their decreasing dose.

The patient withdrawn meant that their glucose levels were too high for the study. They could no longer be normalized on oral medication, and they had to be discontinued.

Twenty-nine percent of patients on placebo either decreased or discontinued their need for medication, while 43 percent of the orlistat patients decreased or discontinued their need for medication. Ten percent of orlistat patients worsened during this study. Twenty-five percent of placebo patients worsened during this study.

We looked at hemoglobin A1c's in the whole population, as well as those patients who were under worse control when they started, with a hemoglobin A1c of at least eight percent. During the one year of treatment, there was a small decrease in the placebo group and a greater decrease in the orlistat group. The absolute difference between treatments was about .5, going down on average from patients who were on placebo of 8.65 to 8.60, and those patients on orlistat from 8.76 to 8.2, and again, these differences were significant, and they were maintained long term.

The results here are similar to what you see when you add acrabose (phonetic) to sulfonylureas, and acrabose, as we know, is an alpha glucosidase inhibitor that pretty much does to carbohydrates what orlistat does to fat.

And finally in this study we looked at lipids, and based on least square means differences between placebo there were improvements compared to placebo for total cholesterol, LDL cholesterol, and triglyceride.

Orlistat's safety and tolerability profile was established during two years of treatment. A total of 7,000 patients and volunteers have

participated in our global development program, with over 5,000 patients receiving orlistat. The data show that orlistat is generally well tolerated during chronic administration.

Since our Phase 3 program is very large, I'll present most of our data from that database.

Close to 2,200 patients received one full year of orlistat treatment with over 1,500 patients on the recommended dose of 120 milligrams three times a day. Seven hundred and 77 patients received two full years of orlistat treatment, with over 500 of those on the recommended dose of 120 milligrams three times a day.

There are several very important pharmacokinetic and pharmacodynamic characteristics of orlistat. Orlistat is minimally absorbed with less than one percent of an administered dose available systemically, and what little may be absorbed has no measurable effect on systemic lipase activity, and in over two full years of monitoring, there was no evidence of accumulation of the drug.

Withdrawal rates were comparable between the orlistat group and placebo group in one year and in year two, and in fact, they were rather modest for weight loss studies. The differences between

withdrawals for adverse events on that first sub-line that you see there is made up mostly of GI adverse events, which I'll discuss soon.

The withdrawal rate, as we said, in the second year was very, very similar for both orlistat and placebo, with no major differences seen.

Serious adverse events were seen in approximately six percent of patients on both orlistat or placebo in both year one and in year two. Most of these were sporadic and isolated occurrences and had no discernable pattern.

As you know, there was an imbalance in breast cancer cases reported during the Phase 3 program. Breast cancer is a serious and common disease, with one out of nine women developing it during their lifetime. Later this morning we will provide in an open and thorough manner a detailed presentation of what we have found regarding the imbalance of cases.

Now looking at non-serious adverse events, we defined the most commonly occurring adverse events reasonably associated with orlistat as those occurring at a rate of at least five percent in the orlistat group and being at least twice as frequent as in the placebo group.

When we looked through our entire database, the only criteria that met these -- the only adverse events meeting this criteria were in the GI tract and probably secondary to the pharmacodynamic action of the compound.

To better characterize these findings, a dictionary of standard terms was provided for investigators for consistency.

These are the events that met the criteria that I just talked about. They occurred in the first year with an incidence of up to 27 percent or as low as eight percent, but importantly, the withdrawal rate due to these adverse events was very low, less than two percent in general, and if you look at the second year of treatment, they were marked low as compared to the first, and the withdrawals due to these adverse events in the second year were generally below less than one half of one percent in all of the categories.

This very low withdrawal rate showed that the events were well tolerated, and the reason they were well tolerated is due to the fact that the majority were mild in intensity, limited to one or two episodes per patient, and occurred generally early in the study.

We looked at other adverse events

regardless if they occurred more frequently on orlistat or not, and on this slide, although it may be a little bit hard to see, the very top line is abdominal pain. One might predict that orlistat would, in fact, produce a significant increase in abdominal pain, but 16 percent of the placebo patients had abdominal pain compared to 20 and a half percent of the orlistat patients.

Dropping down to adverse events, such as nausea, infectious diarrhea, or dyspepsia, the adverse event findings were virtually identical. In year two all adverse events were lower in both treatment groups, and there was no pattern in favor of one group or the other.

We looked at adverse events outside of the gastrointestinal system and found no major differences between treatment groups. General laboratory assessments were done throughout the studies, and for standard assessments no clinically meaningful differences were seen.

In addition, electrocardiograms and gold letter ultrasounds were done which did not identify any clinically meaningful findings.

Renal stone development based on the potential increase in free fatty acid in the colon was

evaluated. During year one of the studies, there was an incidence of .2 percent in the placebo group and .8 percent in the orlistat group. During year two of the study, there was the same in both the orlistat and the placebo group.

Because orlistat selectively inhibits the absorption of fat in the gastrointestinal tract, we prospectively examined levels of fat soluble vitamins in all of our Phase 3 studies. To fully characterize the effect of orlistat, we discontinued any vitamins prior to study entry. Vitamins were measured at entry and throughout the study period, and the levels were sent to a centralized laboratory.

If a patient had two consecutive measures below the lower range, a standard multivitamin, over-the-counter preparation was given. What follows are the results for each of the vitamins we evaluated, and the data set is from our two year population.

Here is Vitamin A levels over two full years. The shaded area is the normal, the upper and lower boundaries of the reference ranges that we used. We see that in this data there is no difference at all between the orlistat and placebo group, and in fact, over time there appeared to be a small increase in Vitamin A levels.

Turning to Vitamin D, there were small differences between treatments at the start of the studies, and the orlistat and placebo patients were generally parallel to one another over time. There was an average mean decrease of approximately eight percent on orlistat patients, and this was statistically significant.

Looking at the evaluation when we look at people who had two consecutive low values, we see that a large number of placebo patients, in fact, 13 percent, actually had two consecutive low values, and that compares to about 18 percent on the orlistat group. The majority of those patients received supplementation, and the last value in the study was about the same, 92 percent in the placebo group and 90 percent in the orlistat group, as being normal.

We did a special study, that one year, that study that I said we did with primary care physicians, which was a two years study. We measured ionized calcium and we looked at PTH values believing that that would be the first indicator of physiologic consequences to these relatively modest decreases in Vitamin D.

We see no differences for ionized calcium or PTH between treatments or within treatments over

the two full years.

Vitamin E is frequently reported as a ratio to lipid levels since lipids are the carrier molecule in the blood. Because the major portion of Vitamin E is carried in LDL cholesterol molecule, any significant change in LDL levels will change circulating Vitamin E levels, and as we saw before, there was about a ten percent decrease in LDL cholesterol.

Therefore, to show you the data as a ratio, we see no obvious physiologic consequences to the decrease in Vitamin E, and in fact, probably the majority of the decrease that you could see is due to the decrease in LDL cholesterol levels, and we don't believe there's any physiologic consequences to these changes.

Beta carotene also was evaluated over two full years. During the four week placebo lead-in period, both groups had an increase, and then after randomization, there was a decrease in those patients on orlistat, and there was a plateau of the effect with a new steady state being reached. By the end of the treatment, although there were differences that were statistically significant, those patients on orlistat, in fact, had a value that was actually

higher than it was prior to starting treatment.

Vitamin K was evaluated indirectly by prothrombin time, and again, over two years of treatment we saw no differences.

When looking at vitamin levels which fell below the reference ranges, supplementing patients with over-the-counter multivitamins normalized most patients, and by the end of the study there were few differences between the orlistat and the placebo group.

So to summarize our effects on vitamins, all mean vitamin levels remained within the reference range. There were modest decreases in Vitamin D and beta carotene, which were statistically significant. Multivitamins reversed most of these decreases, and as was discussed at the last Advisory Committee, we recommend that all patients receiving orlistat should also receive multivitamin supplementation while they're taking treatment.

To summarize the safety of orlistat in general, there were very few clinically significant findings. Most were well characterized and secondary to the pharmacologic effect of the drug. They were generally limited to the gastrointestinal tract, mild to moderate in intensity. Most of those occurred

early in the treatment, and there were few withdrawals.

Other issues, such as vitamins, we just discussed, and later today we'll discuss the imbalance of breast cancers identified during the study.

To summarize efficacy, treatment with orlistat produces sustained weight loss. It diminishes weight regain, and it's effective long term.

And finally, I'd like to conclude with a review of the effect of orlistat treatment in improvements in obesity related risk factors.

In many patients, orlistat treatment improved lipid profiles, decreased elevated blood pressure, decreased insulin, glucose, and C peptide values, normalized people with abnormal oral glucose tolerance testing, and improved glycemia control in diabetic patients.

Now, Dr. Colman from the FDA, I believe, will make his presentation.

CHAIRMAN BONE: Before Dr. Colman speaks, do members of the Committee or the guests at the table have specific questions regarding the presentations of any of the sponsor's speakers at the moment?

Okay. Dr. Davidson.

DR. DAVIDSON: You know, in some of the initial comments, it was well stated by Mr. Atkinson from the American Obesity Association that the burden of obesity and diabetes is a lot more in minority patients, and my question to you is, you know, what is the percentage of minorities in your study because in your slide it show that it is negligent. It is less than one percent.

Knowing today that one of every two newly diagnosed patients with diabetes happen to be minorities, and among those minorities, Mexican Americans and the Latino group, especially males, have increased tremendously their weight past the age of 40. You know, I wonder how many Latinos are included, the percentage of African Americans and Asian Americans.

DR. HAUPTMAN: Can I have the slide on, please?

This is based on the entire efficacy study, not just -- this is a combined U.S./non-U.S. program. So these data represent the entire population. There was seven percent on orlistat for African Americans, 4.8 percent on placebo; 2.2 percent of Hispanic. The actual numbers though of those studies done in the United States was about twice that

amount. So it was about 15 percent of African Americans in the United States, the studies done in the U.S., and about seven percent.

But we can show you the effects in this subpopulation if you'd like to because we did look at this. We've broken out -- although the numbers are small, we did break it out to look if there is an effect in this population.

DR. DAVIDSON: With that small percentage, is that possible to have any conclusions?

DR. HAUPTMAN: The trends we could look at to show you.

DR. DAVIDSON: Okay.

DR. HAUPTMAN: Now, we did the studies across the United States. We did a number of studies in Southern California and Texas, and quite frankly, we were surprised that we didn't get more minority patients than we actually got.

Slide on, please. Okay. Actually I was looking for the slide that looked at body weight. Okay. Here it is.

This is looking at the end of one year, comparing the white population to the black population and Hispanic population, although for the black and Hispanic population the numbers are smaller and, in

fact, probably should be studied to a greater extent. The trends that we see here are very similar to the trends that we see overall, and I believe that the literature shows that for the Hispanic and the black population, weight loss programs are usually not as effective as the exact same similar program in the white population.

So this is a trend that I think is very valuable.

CHAIRMAN BONE: All right. Additional questions directly related to the content of this earlier presentation? I think Dr. Marcus, Dr. Ellis, and then Dr. New.

DR. MARCUS: I presume that now another year, year and a half has passed since the termination of your two year study. I just wonder if you have any information as of March of 1998, what the residual effect of having participated in the trial is in terms of current body weight.

MR. HAUPTMAN: We don't have that data.

CHAIRMAN BONE: Dr. Ellis?

DR. ELLIS: Obviously you've generated large serum banks from these studies since you did a lot of these serum analyses for vitamins, et cetera. Have you gone back and looked at estrogen levels,

particular in the post menopausal group to see what happened during treatment?

DR. HAUPTMAN: Yes, we did, but I think that that would be part of a later presentation. So I'd like to hold back what we have and present that later.

DR. ELLIS: Thank you.

CHAIRMAN BONE: Thank you, Dr. New.

DR. NEW: Could I just ask you whether the weight loss reflected the diminished calories as evidenced by the fecal loss of fat?

DR. HAUPTMAN: It was very similar. The average amount of fecal fat that was lost over two full years was approximately 20 grams per day during one year and two years. If you actually go back and do the math using nine kilocalories per kilogram of weight loss per gram of fat, it actually becomes quite similar.

I know there are other opinions as to how orlistat may work, but if you look at fecal fat, figure out the amount of calories, subtract it over the length of time for six months, it works out to be almost the same as you would expect.

CHAIRMAN BONE: Thank you.

Dr. Davidson, did you have another

question about this?

DR. DAVIDSON: One more question. You know, obviously maybe we can do the calculation, but if you have the percentage of nonresponders. You know, you show a lot of the responders' data, but what is the percentage of nonresponders in general in the trials?

DR. HAUPTMAN: If you use a five percent weight loss as the cutoff for nonresponders, using the difference from baseline, not from initial, it comes out that it is an average of around 40 percent, I believe, because what we showed was the 57 percent or 60 percent of patients who lost at least five percent or greater. So then the assumption is that all of the other patients were less than five percent.

DR. DAVIDSON: And from placebo? You know, because it looks like you did a lot better than Dr. Rena Wing with all of the studies she did. You did better with the placebo trial than from placebo was the nonresponder rate.

DR. HAUPTMAN: Placebo was greater. If I remember the numbers correctly, it was about 26 -- it was around 74 percent were nonresponders were placebo.

CHAIRMAN BONE: Thank you.

And Dr. Cara had a question about the

presentations.

DR. CARA: You presented data for the second year which was designed to evaluate the efficacy of orlistat at preventing weight regain. Have you done any studies to look at whether you can continue weight loss during second year of therapy?

DR. HAUPTMAN: We didn't do it as part of our 3(a) program, but I believe those studies are planned for 3(b) or post marketing studies where, at the end of the first year, the diet is still the hypocaloric.

DR. CARA: And how did you monitor compliance in patients?

DR. HAUPTMAN: The standard way of monitoring compliance was based on capsule count. So the majority of the patients we just counted the capsules. They were given blister packs.

CHAIRMAN BONE: Thank you.

The next presentation will be made by Dr. Colman from the Division of Metabolic and Endocrine Drug Products.

DR. COLMAN: My presentation should be no longer than 15 minutes, and for this I expect Dr. Bone to give me the time out signal so that I will stop.

CHAIRMAN BONE: Dr. Colman, we want to

hear every word you have to say here.

(Laughter.)

DR. COLMAN: Okay. I'm going to focus this morning on efficacy and specifically look at the one year weight loss data and then talk a little bit about the effects of the drug on the major co-morbidities, those being lipids, blood pressure, fasting glucose and insulin.

Just as a reminder, there were seven Phase 3 studies conducted in this program, and they ranged from one year to two years, and they compared placebo with 30, 60 or 120 milligrams three times a day of orlistat.

The studies on the bottom in yellow I will not be discussing. This was a weight regain study, and this was a study in obese diabetics, and I will not be discussing these data. I'm going to limit my talk to the five studies shown here in white, and the reason for that is these five studies were very similar in design. They had very similar patient populations, and individually the weight loss results were comparable across studies.

So, again, I'm going to show you pooled data from these five studies and limiting it to this, the first year of treatment, and because the 120

milligram dose is proposed for marketing, I will restrict my comparisons to placebo versus orlistat 120.

This slide gives you an idea of the number of patients involved in the one year study. There were over 1,500 patients randomized to orlistat, 120 milligrams. There were over 1,000 patients randomized to placebo, and on the second line you can see the number of patients who completed one year of the study. This is roughly a 68 percent completion in the orlistat group and a 62 percent completion in the placebo group, fairly good completion rates.

Again, the two groups, placebo and orlistat 120, were very well matched at baseline. There were no significant differences for demographics, and again, by and large, we're talking about a Caucasian female population that was studied. The mean age was about 44 years. Almost 40 percent of these women ere 45 years of age or older at the time of randomization. This will become more relevant as we get into the breast cancer data, but something to keep in mind.

The mean BMI at entry was 35 kilograms per meter squared. For those of you who are more comfortable with pounds and kilograms, the initial

weight on average was almost 100 kilograms or 220 pounds.

Before I get into the actual weight loss data, let me quickly remind everyone of the two efficacy criteria that are outlined in the division's obesity guidance document. The first criteria is based on group means and simply says the mean percent weight loss in the drug treated group should be at least five percent greater than the weight loss in the placebo group. So again, that's the analysis based on the means.

The second analysis is based on a categorical or responder analysis, and that simply states that the proportion of patients who lose at least five percent of their baseline body weight is greater in drug versus placebo, and if either one of those criterion aren't satisfied, the drug would be deemed efficacious.

Now, having said that, let me show you the analysis of the means first. This slide shows the mean percent change in body weight over a one year period, 52 weeks, percent change shown along the Y axis.

Some nomenclature I'd like to point out first. Initial body weight refers to the weight

before participation in any aspect of the study. You'll recall there was a four week placebo lead-in period that all patients took part in. After that four week period, patients were then randomized to either drug or placebo. The weight at this point is referred to as baseline body weight, and it's important to keep these two separate.

I will be restricting most of my comparisons to baseline as I feel that is a more relevant body weight point, since this is the point where people were randomized to drug or placebo, and we're trying to see what this drug does to placebo. So I think the baseline body weight is relevant, and I'll be speaking primarily with this in mind.

You can see that during this four week lead-in period the average weight loss was about two and a half percent. After they were randomized to drug or placebo the lines quickly diverged. There was a continued loss in the orlistat group such that by the end of one year this orlistat treatment group had lost about six and a half percent of their baseline body weight, whereas the placebo group lost about three percent of their baseline body weight, a difference here of roughly three to four percent.

Now, let me show you some data from the

categorical analyses. This first slide shows the percent of patients who lost at least five percent of baseline body weight, again, baseline body weight, not initial. Orlistat is in white; placebo is in blue.

You can see here that there were significantly more patients who were treated with orlistat who met this five percent mark when compared to placebo. These actual percentages are 57 percent versus, I believe, 31 or 32 percent, and again, they were statistically significant.

Looking at the second analysis, which is using a ten percent cutoff, here again we see that there were significantly more patients who were treated with orlistat who achieved this ten percent mark than those patients on placebo. Again, the actual percentages are much lower than those for the five percent cutoff, but nonetheless they were greater for orlistat versus placebo, 27 versus 12 percent.

I'd like to shift to show you a little bit of the co-morbidity data. I should mention at this point that by and large if you looked at the group means, at baseline these patients were not hypercholesterolemic. They were not hypertensive, and they were not diabetic. I believe the average total cholesterol level was about 200 milligrams per

deciliter. The HDL was about 45 milligrams per deciliter, and the blood pressure was, I believe, 123 over 79. So that's important to keep in mind as we look at changes that take place.

And furthermore, the randomization was quite successful. There were no significant differences at baseline between these variables between the groups.

So if we look at the lipid data first, this slide shows the mean percent change in the various lipids from baseline to year one. Again, placebo is in light blue, orlistat in white, percent change along the Y axis, total cholesterol, LDL, HDL, and TG shown here.

If we look first at total cholesterol and LDL cholesterol, and let's look first at the placebo response, we see that actually relative to baseline there's an increase in total and LDL cholesterol in the placebo groups. It's not very large, five percent or so, but there is an increase from baseline, and again, that reflects the paradigm where they started off initial. Everyone lost weight, and then they started at baseline.

In contrast, the orlistat treated subjects lost, had a small reduction in total cholesterol and

LDL cholesterol such that when you compare the differences between the two groups, they were statistically significant.

If we move to HDL cholesterol, we see that the average levels increased in both groups, actually increased to a greater extent with placebo than orlistat, and triglyceride levels on the whole did not change much in either of the two groups.

Now, the next slide looks at the lipid data in a little different manner, and it doesn't look at the means so much. It's broken down by category of weight loss. It shows the mean percent change in lipids by degree of weight loss over the one year period.

The weight loss categories are less than five percent weight loss, between five and ten percent weight loss -- that should be a minus sign here -- and the largest weight loss category is ten percent or more. This also should be underlined here. So basically three different weight loss categories, losing weight as you go in this direction and the different lipid parameters shown here.

Let me just show you if we focus on total cholesterol first and look at the placebo response. You would expect that if a patient were to lose

increasing amounts of weight their cholesterol would go down in a graded manner. We don't see that with placebo until you get up to the ten percent weight loss.

In contrast, orlistat does have a graded, small but graded, continued reduction as they lose more weight, and the same pattern was seen with LDL cholesterol.

You will recall on the previous slide the mean levels of HDL both increased with drug and placebo, and that is reflected in this analysis as well. Irrespective of treatment here, as patients lost more weight their HDL levels went up and the absolute increases were greater in placebo than on orlistat, and again, the mean level was higher in placebo than orlistat in the previous slide.

Now, interestingly enough, triglyceride levels, the mean levels didn't change much at all on the previous slide. However, when you look at the changes by weight loss category, you see again that in both groups there was a rather nice reduction in triglyceride levels as patients lost more weight.

Moving along to blood pressure, this slide shows a mean change in blood pressure over one year, for systolic blood pressure and diastolic blood

pressure. I'd like to point out the Y axis is in millimeters of mercury, and it's rather narrow. It runs from zero to 0.6 and zero to minus 1.2. So we're not talking about large changes here.

Much like total cholesterol, the placebo group actually had a small increase in systolic and diastolic blood pressure from baseline, whereas the orlistat group had small reductions in both systolic and diastolic blood pressure.

Looking at the differences between the two represents a minor clinically beneficial effect, and it was statistically significant.

I should probably point out the significance here. Keep in mind that these are very large sample sizes, and that undoubtedly does play into the statistics and remind people -- I'm sure they're aware -- to not confuse statistical significance with clinical significance.

This slide shows the mean change in fasting glucose over one year. Again, the Y axis, millimole per liter, is relatively narrow, zero to 0.08. We can see the placebo in blue. There really is not much going on here. Actually by the end of the year it is right back to baseline.

Orlistat treatment did have a greater

reduction in fasting glucose, slight upward trend here towards the end of the one year. Nevertheless, there was a small, favorable effect in the direction of orlistat which was unlikely to be due to chance.

And finally, for the co-morbidities, this shows the mean changes in fasting insulin. Again, picamoles per liter on the Y axis, and this is a similar pattern that we just saw with fasting glucose. Placebo, it didn't have much change. It actually went up, and they were slightly above baseline at the end of a year. Orlistat had a reduction, came back up, another small reduction. Again, by the end of a year there was a small relative improvement in favor of orlistat.

Also important to keep in mind, by and large these patients were not diabetic. Again, this was statistically significant.

So to summarize the weight loss efficacy, I showed you an analysis based on the means. I showed you categorical analyses. If we look at weight change from baseline, not initial, but baseline, the placebo group had about a three percent reduction. There should be a minus sign here. Orlistat had about a six percent reduction from baseline body weight, and obviously the difference here is three percent.

In the categorical analyses, orlistat, there was significantly more orlistat treated patients who lost at least five and ten percent of baseline body weight, and these were statistically significant.

If I were to sum up the effects of drug treatment on the major co-morbidities, I would have to say that there were small to modest improvements in the individual co-morbidities, and if one individual were to accrue small benefits for multiple risk factors, that might represent a more significant improvement in the overall risk factor profile.

And that concludes my discussion.

CHAIRMAN BONE: Thank you, Dr. Colman.

Are there questions from the Committee members or guests regarding the particulars of Dr. Colman's presentation?

Dr. Davidson.

DR. DAVIDSON: If you sub-analyze the lipid changes, you know, with the HDL increase in the placebo group, is there any real significant differences between placebo and drug?

DR. COLMAN: You mean were those broken down by weight category of weight loss?

DR. DAVIDSON: In general, because, you know, if you look at the HDL increase, it seems like

it would be a washout, you know, on the total lipid profile. Is that correct or am I incorrect?

DR. COLMAN: If I had the slide I could -- is the slide still on there?

CHAIRMAN BONE: I thought you showed a rise in HDL and a decline in LDL.

DR. DAVIDSON: Right. There's an increase in HDL, more in the placebo --

DR. COLMAN: Right.

DR. DAVIDSON: -- than it is in the active drug, and I wonder if that increase will wash out the other benefits of the lipid profile.

DR. COLMAN: You're talking specifically about the radio of LDL to HDL.

Yeah, I think the company showed that. You might want to.

DR. HAUPTMAN: Yeah, it was -- I'm not sure that I need a slide.

CHAIRMAN BONE: This is Dr. Hauptman speaking now.

DR. HAUPTMAN: Sorry.

Yes, when you looked at the LDL to HDL ratio there was a decrease of about 50 to 100 percent greater decrease on the orlistat patients. I showed patients who had the LDL/HDL ratio greater than 3.5 to

start. There was like a .46 decrease in the placebo group and a .66 decrease. So it was about a 50 percent greater.

The HDLs increase in both the placebo and the orlistat group, but it was outweighed by the much greater decrease of LDL. So as a ratio, looking for improved cardiovascular risk, there still seemed to be the benefit of a much greater decline in the LDL/HDL ratio.

DR. DAVIDSON: Thank you.

CHAIRMAN BONE: Thank you, Dr. Davidson.

I think Dr. Sherwin was next.

DR. SHERWIN: Yeah. Dr. Hauptman, while you're there, I'm just curious. Did the company ever look at post perineal triglycerides since it might affect both the absorption and the removal?

DR. HAUPTMAN: Yes, we did. Let's see if I can find Dr. Guerciolini from our Clinical Pharmacology Department who did some of those studies, and we do have information that might be useful.

DR. GUERCIOLINI: Dr. Guerciolini from Clinical Pharmacology.

K-46, please.

We have done study evaluating the potential effect of orlistat on sustaining lipases.

If you have an effect on sustaining lipases, the most dramatic effect you will see, a dramatic increase in post perineal triglyceride.

We have done two studies addressing this. On an eight week study with multiple doses of orlistat, post perineal triglyceride profile were reduced of 20 percent after a fast rich mean.

On the systemic lipase study -- K-46, please. Slide on -- we evaluated post perineal triglyceride profile under the internal condition of the drug. You can appreciate here that after a fast meal, administer at time zero, the post perineal triglyceride curve follow-up for 12 hours is over impossible (phonetic) between orlistat and placebo, testify and corroborating the finding that no effect on systemic hepatic and lipoprotein lipases were observed with orlistat.

Slide off.

CHAIRMAN BONE: Thank you.

Other questions for Dr. Colman?

This would be Dr. Hirsch.

DR. HIRSCH: Dr. Colman, did you have any opportunity at all to review the year two data? Would you comment on those, namely, in the weight category exactly what was happening with those who continued

treatment with orlistat for two years?

DR. COLMAN: Well, as far as the weight itself, there was a -- the lines clearly -- both lines clearly were trending upwards after the one year towards the two year. The relative position of the two lines was maintained such that by the end of two years the absolute reduction in weight was less, but the relative differences between the two lines was basically the same.

DR. HIRSCH: And your prediction as to when they would both return to baseline would on the basis of that trajectory?

DR. COLMAN: Well, that's hard to say. I mean if they stayed in a clinical trial and they may not. Once they're out of the clinical trial, that's really what is important, but we don't know.

DR. HIRSCH: So staying in the clinical trial would be the optimal situation for reducing the trajectory, if they were not in the clinical trial, assumedly. So it looks to me that by three, three and a half years they'd be back to where they started from. Is that roughly correct?

DR. COLMAN: Yeah.

DR. HIRSCH: Both groups.

DR. COLMAN: I wouldn't argue with that.

DR. HIRSCH: Even with continued treatment.

CHAIRMAN BONE: Maybe the solution to the problem of recidivism amongst our patients would be to have all of the patients in Phase 4 trials.

DR. HAUPTMAN: May I make just one comment? That we have to recognize that second year was not on a hypocaloric diet, and clearly clinical practice would be different. When a patient began to regain weight in a clinical practice, they would then go back on a hypocaloric diet. The second year of our studies was designed to test the hypothesis as opposed to necessarily the clinical utility.

DR. HIRSCH: I noted that fact, Doctor. You may wish to comment on what I'm now going to say, namely, that demonstrates that the major effect after one year is dietary and not drug.

DR. HAUPTMAN: Actually I can't agree with that. I think that the differences between treatments were very much continued during that second year, and the three percent difference that you saw, for example, when you look at baseline to treatment in the first year was, in fact, exactly the same, if not greater.

But I agree with you that patients require

continue follow-up either in structured out-patient situations because you know certainly much better than me the chronicity of obesity.

DR. HIRSCH: I just want to comment that the key to combatting recidivism with this drug is diet and not drug simply because of what you said.

DR. HAUPTMAN: I think it's really a combination of multiple things, diet, exercise, additional benefits of pharmacologic therapy, not just one thing. I agree with that.

DR. HIRSCH: I guess it's a matter of interpretation.

CHAIRMAN BONE: Yeah, I think we'll be discussing this sort of point at some length this afternoon.

Were there other specific questions related to Dr. Colman's presentation?

(No response.)

CHAIRMAN BONE: If not, we'll take our scheduled intermission and try to start up in about ten, 12 minutes.

(Whereupon, the foregoing matter went off the record at 10:22 a.m. and went back on the record at 10:44 a.m.)

CHAIRMAN BONE: The committee will be in

order again.

We're going to hear from the sponsor with regard to the breast cancer problem.

Just one moment, please.

The first presentation will be by Dr. Huber?

DR. HUBER: Huber, Martin Huber.

I'm Martin Huber, a clinical oncologist with Hoffman-LaRoche.

As noted by Dr. Hauptman during the safety presentation, imbalance in breast cancer cases was identified at the unblinding of the Phase 3 clinical program. Following this observation we have conducted an intensive review of the data. What we'd like to discuss with you today is to summarize the findings regarding this imbalance in breast cancer cases.

First, it is important to note that when we looked at the serious adverse events associated with cancer, it was not a major discrepancy between the arms overall for all cancers with regards to treatment or with regards to tumor type, with the exception of breast cancer. For breast cancer nine cases were identified on the orlistat, 120 milligram, arm, one case on the patients receiving orlistat using 30 or 60 milligrams, and there was one case on the

placebo arm.

Of importance though, no case of breast cancer was identified in any of the 1,752 women who were less than 45 years of age. Based on this, and following discussion with the FDA, we chose to focus all subsequent analysis primarily on women at least 45 years of age as this was the at risk population.

This imbalance in breast cancer cases was quite unexpected at the unblinding of the trial. First of all, obesity, if anything, is a risk factor for breast cancer. There was nothing to suggest that a decrease in weight would be associated with an increased finding of breast cancer.

Additionally, extensive preclinical data had shown on evidence of an increase risk of breast cancer. Therefore, we felt that there was not an issue with the Phase 3 program.

And finally, among the 917 women in the Phase 2 program of which 652 had received orlistat either 30 or 60 months, there were no cases of breast cancer reported.

What we chose to look at then were possible explanations for this imbalance. For the purpose of our discussion today, we're looking at four broad mechanisms which could account for the observed

imbalance. The first is causality. For the purpose of our discussion today we'll focus on this is a classic initiator, such as a genotoxic carcinogen.

Second, another mechanism that could account for the imbalance would be stimulation of a preexisting tumor.

Third, a detection effect. In other words, changes in the patient, such as accelerated weight loss, leading to an increased detection of breast cancers. However, this phenomenon, the detection effect, would not be necessarily limited to weight loss alone. It could be due to changes in health seeking behavior, due to differences in GI side effect profile. It could be due to changes in mammographic density. We don't have any specific speculation, but I think it's just important to note that this could be of any various reasons to cause this.

Finally, chance could explain this imbalance, but it would be only considered after the other hypotheses were fully evaluated.

To assess this imbalance we set out to explore what additional evidence we could gather. First, we collected surveys of women who were at least 45 years of age. The reason we had done this is

because one and a half years had elapsed since the end of several of the trials, and we sought to identify whether any additional cases of breast cancer had occurred.

Next, based on this data we asked epidemiologists with expertise in breast cancer, including two that were recommended by the FDA, to review this data.

We also did a complete review of our preclinical data, and then finally we collected all relevant information on the breast cancer cases. We collected pathology slides, reports, mammography films and reports, and clinical evidence we could obtain. This material was reviewed by experts in breast cancer from the fields of oncology, pathology, and radiology.

To briefly show you how the surveys were conducted, we looked at women who once again were at least 45 years of age who participated in the seven Phase 3 trials. The purpose of the first study was to identify any additional cases of breast cancer.

If orlistat was expected to have caused breast cancer, what we would have expected to see was additional new cases of breast cancer occurring during this period or even increasing during this period. We, in fact, collected information on almost 90

percent of the 1,642 patients at risk, and among these 1,642, of these patients three new cases were reported, one on placebo and two on orlistat, 120 milligrams.

Then we performed a second survey, and the purpose of this one was to focus primarily on gathering information on risk factors for breast cancer. As we were conducting this study, an additional case of breast cancer was identified in a patient on placebo.

So when we add up together the reports from the trial and those identified in the survey, we have a total of 15 cases of breast cancer identified. Among placebo, there's a total of three, one during the trial and two during follow-up, and the reason we have an asterisk on this one is as this case was found one month after the cutoff date for the first survey, it will not be included in the primarily epidemiologic analysis, but will be discussed in full detail for other issues, including clinical biology.

The orlistat 30 or 60 group, we had a total 316 women at least 45 years of ago, in which there was one case of breast cancer identified, and among the 747 women at least 45 years of age we had 11 cases on the orlistat 120.

So what I'd like to do now is turn it over to Dr. James Schlesselman, who will review the epidemiology findings.

CHAIRMAN BONE: I think there may be some questions from members of the Committee regarding the specifics of this presentation. These are awfully important. So --

DR. HUBER: Good.

DR. HIRSCH: The preclinical data, I'm curious as to whether or not you ever did animal studies in which animals were given known carcinogenic agents, nitroso (phonetic) compounds or whatever, and with or without Xenical.

DR. HUBER: Dr. Tim Anderson from our preclinical.

DR. ANDERSON: No, we did not do additional studies beyond those which I will present this morning, but I can readdress that question with you after you see the preclinical information.

DR. HIRSCH: Thank you.

CHAIRMAN BONE: Yes, that's Dr. simon.

DR. SIMON: Did you do a follow-up survey on the women who were in the Phase 2 studies?

DR. HUBER: No, sir.

CHAIRMAN BONE: Thank you.

Additional questions? Dr. Critchlow.

DR. CRITCHLOW: Could you give us a little more information about the questions that were in the survey? Did you ask about whether they had sought mammograms and if so, what was the mammography rate among the cases in the controls?

DR. HUBER: Yes. Actually if you could hand me the -- with regards to the survey, if it will help the Committee, if you go to Volume 3 of your briefing document, page 59 is actually the detailed procedures for conducting the survey, and then with regards to your specific question, if you go to page 68, it gives you the actual -- this is a blank copy of the survey that was administered, and it has all of the information that's included.

CHAIRMAN BONE: Which page under which section? Final survey report?

DR. HUBER: Yes.

CHAIRMAN BONE: There are several sections which are independently numbered.

DR. HUBER: Okay. I apologize. But look at the number on the top right-hand corner.

CHAIRMAN BONE: Oh, the top right-hand corner. I'm sorry.

DR. HUBER: Go to page 68 for the actual

survey itself, and what was asked in that questionnaire was a series of questions, and I think what I'd call your attention to on the -- let's see. There was a question regarding cancer on page 70. There was a question, "Have you suffered from any serious illness, for example, heart disease, cancer, diabetes," et cetera, "since you finished this study?" And then it would lead to the specific track if they had cancer.

On the preceding page, there was a question about have you had any of the following screening tests, and it included mammography.

With regards to mammography specifically, we have some data on this. When we conducted the second survey looking at risk factors, we did try to collect some information on the mammography habits in the two populations. Overall about 80 percent of the patients on each arm did have a mammogram done previously.

Do we --

DR. CRITCHLOW: During the survey period or during the post?

DR. HUBER: Well, in the survey they --

DR. CRITCHLOW: Post trial period?

DR. HUBER: -- stated they had at least one

mammogram. Now, whether it was during the trial or during the survey follow-up, it's not necessarily -- you know, it's unknown, but we do have in the second survey then -- we collected information on how frequently they were getting mammograms, either annually or every two years.

DR. CRITCHLOW: And the difference or lack thereof between the cases and controls in terms of percentages receiving mammograms?

DR. HUBER: I don't think we looked specifically at cases. We did not necessarily do case versus control. We looked at the difference between the two arms.

DR. CRITCHLOW: I mean drug versus --

DR. HUBER: Right. Dr. Schlesselman was going to present some of that information, I believe. I don't know if you want to see it now or during the presentation.

CHAIRMAN BONE: Yes. Dr. -- I'm sorry. It was Dr. Siegel.

DR. SIEGEL: Of the 652 people on the orlistat during Phase 2, how many were on the 120 milligram dose and how long were they on it?

DR. HAUPTMAN: Could you please repeat the question?

DR. SIEGEL: Sure. I'm just trying to get more information about the Phase 2 trials. There were 652 patients on the study drug. Of those how many were on the 120 milligram dose and how long were they on that?

DR. HAUPTMAN: The Phase 2 studies went generally from three months to six months, and the average dose was around 120. I would estimate that somewhere around 75 percent of those patients on orlistat had a dose of 120 or greater.

CHAIRMAN BONE: All right. Thank you.

And, Dr. Sherwin, questions about the first presentation?

DR. SHERWIN: Yes. It relates to the detection of another placebo patient after the first survey. Did I get that correct?

DR. HUBER: Yes.

DR. SHERWIN: There was a second survey.

DR. HUBER: Correct.

DR. SHERWIN: Now, do we have data after the second survey? In other words, I was just surprised that it was excluded from the analysis even though you already had another survey that had other data.

DR. HUBER: The second survey did not ask

a question about new cancers or breast cancers. That case was identified around that period. Essentially it was a spontaneous report that came in of a new diagnosis. So since that was not --

DR. SHERWIN: You didn't have a control group for that.

DR. HUBER: Right.

DR. SHERWIN: I see.

CHAIRMAN BONE: No denominator.

DR. SHERWIN: No denominator. Fair enough.

CHAIRMAN BONE: All right. Then we'll -- Dr. Cara, is this a question about the first?

DR. CARA: Yeah, about the questionnaire. It seems to me the only way that an abnormality would have been recognized or picked up was if the patient, in fact, had had a mammogram. That was what the questionnaire was geared for.

DR. HUBER: Well, actually, no, it was for any serious illness, including cancer, and in fact, some of the patients were identified actually during the trial period, and we only had three in the survey, but during the trial period several were also found on clinical exam.

CHAIRMAN BONE: So the questionnaire

really is a rather general questionnaire which doesn't specifically ask did you develop breast cancer, right?

DR. HUBER: No, I mean --

DR. CARA: I guess I have problems the way the questionnaire is designed because I'm wondering if you, in fact, pick up everybody that had an abnormality.

DR. HUBER: Well, our feeling was before we had collected information on 90 percent of these people and we know that 80 percent of them had had a mammogram, that was somewhat sensitive. Also, remember that additional cases that came in through spontaneous reports would have been identified, for example, the third case.

DR. CARA: How was the questionnaire developed? Did you do it in house? Did you seek a consultant?

DR. SACKS: My name is Susan Sacks. I'm a biostatistician/epidemiologist.

The first questionnaire was developed in house and was intended to be a questionnaire that would ask several questions and including it asked had any cancer been found, and then if they answered breast cancer, there were specific questions that were then asked.

I want to clarify a couple of things. On that questionnaire we did determine women who had had a mammogram between the clinical trial period and the survey period.

We then consulted several epidemiologists to help us design the risk factor survey questionnaire, which went out very shortly afterwards. I would say within a month or two, and that was designed predominantly to pick up questions on breast cancer risk factors.

Included in there was a question about mammography frequency, and to address your question, essentially 67 percent of women in the 120 group had reported a mammogram at least every two years. Seventy-one percent of the women on 30/60, and 63 percent of the placebo women, and approximately 13 percent of each treatment group reported no mammography.

So we have a group of women with health seeking behavior, and I want to also clarify that third placebo case was picked up, filled in on that risk factor survey, and because we had cut off a specific defined date with that first survey, we felt that we wouldn't include it in our more formal epidemiologic analyses, although we felt that, you

know, we would at least mention it because had it been orlistat, it would have, you know, generated a lot more interest.

So thank you.

CHAIRMAN BONE: All right. I think there was a final question from Dr. Hirsch.

DR. HIRSCH: You probably said this, but I may have missed it. What percent of the people to whom you sent the questionnaire returned it?

DR. HUBER: We collected it. Well, we didn't actually send it. It was a phone survey, but we got information on 90 percent of the people.

DR. HIRSCH: Ninety percent. Thank you.

CHAIRMAN BONE: All right. The next presentation, I believe, is by Dr. James Schlesselman.

DR. SCHLESSELMAN: Dr. Sobel, Dr. Bone, members of the Advisory Committee, my name is Jim Schlesselman. My appointment is Professor of Epidemiology and Public Health at the University of Miami School of Medicine. I'm also Chief of the Division of Biostatistics at the Sylvester Comprehensive Cancer Center. I'm a consultant to Hoffman-LaRoche.

Apart from my work on the matter before you, I have no financial interest in Roche, nor do I

have any financial interest in orlistat.

Last fall I was asked by Roche to review materials relating to breast cancers occurring in these Phase 3 clinical trials. I, therefore, read their briefing document prepared for last May's meeting of your Advisory Committee, including selected sections of Roche's clinical expert report.

I read three volumes of Roche's resubmission of its NDA last November that are pertinent to breast cancer. I also read reports prepared by the FDA and by consultants to Roche.

I was asked by Roche to place myself in your position as if I were a member of your Committee. I was asked to offer my honest opinion about the findings concerning breast cancer, including the soundness and thoroughness with which the epidemiologic analyses had been done. Roche placed no restriction on how I went about my work or on how I expressed my views.

These were filed in a written report on February 10th this year. The report is part of your background materials.

In that report I expressed my view that cause-effect as a plausible explanation for the excess number of breast cancers occurring in older women

treated with orlistat had been ruled out persuasively on biological ground. By absence of cause-effect I mean that orlistat, in my opinion, is neither a tumor initiator nor a tumor growth enhancer. I believe this conclusion is well supported by preclinical toxicology studies, by findings of mammography, by clinical observations, and by pathology and histopathology.

Presentation of these data will follow later this morning.

I also believe that my conclusion is supported by the epidemiologic data which I would now like to review for you.

This slide shows the number of patients randomized to the three treatment groups, the person-years of follow-up for the three respective groups, the observed number of cases of breast cancer occurring in women 45 years of age or older. There were no cases in younger women, and estimates of relative risk.

These represent the ratio of the observed incidence rates. So, for example, in placebo the rate is 1.4 cases of breast cancer per 1,000 women-years of follow-up, 2.5 cases per 1,000 in orlistat 30/60, 8.2 cases per 1,000 women-years in orlistat, 120 milligram.

So the risk is increased about 1.8-fold in orlistat 30/60 as compared to placebo, about 5.9-fold in orlistat 120 as compared to placebo.

Of course, the relative risk of 1.0 would mean that the two rates being compared are identical, and the 1.0 you see here is simply a comparison of placebo against itself.

I should emphasize that the observed number of cases is small. The relative risks for orlistat in each instance have confidence intervals, 95 percent confidence intervals, which include a relative risk of 1.0. The results are, therefore, consistent with chance at the commonly accepted level of statistical significance.

The analysis presented here is conventional. It accounts for the duration of use by each patient and the follow-up time for each person enrolled.

I would also like to point out that while numerous endpoints have been examined in the clinical trial, no correction for the number of comparisons has been made to the confidence intervals. If an adjustment were to be made for multiple comparisons, the confidence intervals would be wider than what is shown.

This slide shows results which take into account the extended follow-up from the survey that was conducted after the clinical trials had ended. This survey occurred approximately one and a half years after the conclusion of the clinical trials, and you will notice that with extended follow-up the relative rates of breast cancer for orlistat as compared to placebo, in both instances the relative rates or relative risks declined.

You'll also note again that in both instances the confidence intervals cover a relative risk of 1.0.

This is a back-up to the previous slide, and the point I want to emphasize is that with increasing follow-up we have a decline in relative risks.

If an exposure caused cancer by tumor initiation, then one would expect -- certainly I would expect -- there to be no increased risk shortly after such exposure. The reason is that transformed cells have to multiply and the resulting tumor growth sufficiently to reach a clinically detectable stage.

Relative risk should increase over time, not decrease, in this situation.

The decline in relative risk with

increasing follow-up is also inconsistent with the behavior of known tumor growth enhancers, such as hormone replacement therapy and pregnancy. For both of which there is an increased risk of breast cancer which is seen after the stimulus is removed.

Thus, if orlistat were to stimulate tumor growth in a similar manner, one would not have expected all excess cases of breast cancer to be detected during the clinical trial, and there are three reasons for my statement.

First, all women were not under continuous surveillance for breast cancer during the clinical trial.

Second, no method of tumor detection is perfectly sensitive.

And, third, not all tumors would be at the same stage of growth when they were exposed to orlistat. Some, quote, tumors might be a clone of a few dozen cells. Others might be one-tenth of a millimeter in size, others one to two millimeters.

Thus, even with growth stimulation the smaller size tumors would take a longer time to reach a clinically detectable stage of growth than larger tumors. Thus, these smaller growth stimulated tumors would necessarily be detected later in time.

One other point should be mentioned. During the clinical trial there were no breast cancers in younger women, those under age 45 years. One would expect -- I would have expected -- a tumor growth stimulator to have had at least some effect in the younger women.

If one refers by analogy to the former controversy about a possible adverse effect of oral contraceptives on the risk of breast cancer, it is based on an apparently slight increase in the risk of breast cancers in young women, those under age 40 to 45 years.

This slide goes to a question that was asked earlier. For all study groups, about 80 percent of women reported having had a mammogram during the survey period, that is, between the end of the clinical trial and the time the woman was questioned during the follow-up survey, and about 90 percent of women responded to the survey.

Mentioned earlier was the fact that there was a third case of breast cancer reported after, slightly after the survey period, and although this case is properly excluded from formal consideration, I show this slide nevertheless because if the breast cancer had occurred in a woman who had used orlistat

as opposed to placebo, I'm certain that it would have received careful attention and justifiably so, and you will see that inclusion of this third case further reduces the estimates of relative risk.

The next two slides that I'm going to show have results which exclude cases of breast cancer occurring within six months of starting treatment. The FDA's reviewing medical officer, Dr. Karen Johnson, wrote in her review of orlistat that, and I quote, "if there is suitable evidence that an invasive breast cancer lesion is established prior to the start of a study drug, then such a case should be considered preexisting and not suitable for an analysis of association," end of quote.

Dr. Johnson gave as one example of suitable evidence for excluding cases, quote, "invasive cancer diagnosed within six months of study entry," end of quote.

Now, such cases certainly could not have resulted from an exposure that was a tumor initiator. Since the main focus is on orlistat 120 against placebo, I show only that comparison, and during the clinical trial relative risk is reduced, previously, if you recall, from 5.9 to 3.7.

If we include the clinical trial and the

survey period itself, exclusion of the cases occurring within six months of starting treatment, the relative risk for orlistat 120 as compared to placebo is now 2.6, and once again, the confidence intervals cover a relative risk of 1.0.

This figure shows the distribution of the time of occurrence of breast cancers. The distribution of the time of occurrence of all cancers other than cancer of the breast among all participants in the clinical trial, that includes both men and women. The figure in my estimation shows that there's nothing peculiar about when breast cancer has occurred as opposed to when other cancers occurred.

For example, there is no concentration of breast cancers early in the study, which one would expect to occur for a drug that stimulated tumor growth.

If we look only at breast cancer and include the follow-up survey, this shows the distribution of breast cancers. I should point out that yellow represents 120 milligram orlistat; blue represents placebo.

If I may back up to clarify, blue is the placebo case; yellow, 120 milligram orlistat. Blue is placebo, and the violet represents the 30/60

milligram.

Four considerations are used to structure epidemiologic thinking about the reason for an association: cause-effect, bias, confounding, and chance. In view of the size of the Phase 3 trials and the fact that they were randomized, one would not expect baseline imbalances in well established risk factors for breast cancer to account for the excess breast cancers in women treated with orlistat.

This slide confirms our expectation by showing the proportions or percentage of women with history of breast cancer in a mother, approximately six percent across all treatment groups; history of breast cancer in a sister, approximately six percent, and so on. Average age at menarche menopause; average age at first live birth, all of these factors are well balanced among the three treatment groups.

Thus, confounding is almost certainly not the explanation for the breast cancer results.

Professor Demitri Trichopolous (phonetic), former Chairman of Epidemiology at Harvard University, has hypothesized that enhanced detection of breast cancer in women who lose weight accounts predominantly for the excess breast cancers diagnosed in women treated with orlistat. The data are certainly

consistent with this possibility.

In my view, there is presently insufficient evidence to conclude that a detection effect actually occurred. I should note that Dr. Trichopolous stated that, quote, "chance is also likely to have contributed to the observed pattern," end quote, and he also said that the higher frequency of breast cancer diagnosed in women taking orlistat, quote, "has nothing to do with carcinogenesis," end of quote.

The substance of my presentation today began by referring to my conclusion that on biological grounds cause-effect is not a plausible explanation for the excess number of breast cancers in women treated with orlistat. I believe that the epidemiologic results also support this conclusion, namely, that orlistat is not a tumor initiator, nor does orlistat stimulate the growth of tumors of the breast.

In terms of probability, the excess number of breast cancers in women treated with orlistat is an unusual occurrence. They are also comparable with chance.

Now, appealing to chance as an explanation would not be compelling to me if alternative

explanations were not considered and ruled out. The biological implausibility of cause-effect, which is supported by the epidemiologic findings, persuades me to accept chance on the evidence presently available as the explanation for the excess breast cancers observed in women treated with orlistat.

A similar opinion was expressed by Dr. Kenneth Rothman, Professor of Public Health at Boston University, who also reviewed Roche's data and conducted further analyses based upon it.

Dr. Tim Anderson will now discuss the preclinical data on orlistat.

CHAIRMAN BONE: Well, just a minute, please. There are several questions from the Committee members for Dr. Schlesselman. We'll start with Dr. Marcus.

DR. MARCUS: I had naively assumed that your relative risk in the placebo group was compared to some sort of historical standard or some sort of population based evidence. It turns out you were just comparing placebo to itself.

So, of course, I would like to know how your overall experience in the placebo group compared to what would have been expected in the population, and that comes particularly home to me when I saw one

of your most recent slides, epidemiology slide 16, showing the age of menopause across the board for your patients, which was 47, 47.6, and 46.8.

The traditional wisdom in the United States is that the average age of menopause is 51.6 years. So you have a group of people who have about a five year earlier menopause, and I wonder what the impact of that is on overall breast cancer rate, and I wonder if you could clarify those two issues for me.

DR. SCHLESSELMAN: Yes. Firstly, I believe that the best comparison is done internally within the study itself. There are comparisons against the SEER data and IARC data, and Dr. Sacks can present those to you.

DR. SACKS: Right. In your documentation, you have the epidemiology report that was prepared, and in that report we did present the comparisons to SEER plus IARC, SEER for the U.S. women, IARC for our European women.

And if I could have Slide L-5, please. Sorry.

But we -- okay. This is the comparison where you would compare all of the treatment groups to what would be expected in the group of women making up the SEER and IARC databases. You'll see that the

relative risk is lower than in the comparison to placebo.

And if I could have -- this is for the clinical trial period -- and Slide L-6, the next slide, please.

This is -- you can see that the relative risk in the 120 group is now 1.7 when we take into account the clinical trial and survey when we compare to our women in the trial plus the survey period.

CHAIRMAN BONE: So I think you're saying that the experience in the placebo group was less than in the -- than predicted.

DR. SACKS: Yes, but not significantly so. I think --

CHAIRMAN BONE: Well, but I mean this change in the relative risk that you've imputed to the treatment group is obviously -- I mean you have to take that into account.

DR. SACKS: Right.

CHAIRMAN BONE: There was a 50 percent reduction. You said your relative risk was .5 in that slide for the placebo group versus the population; is that right?

DR. SACKS: Yes.

DR. MARCUS: Excuse me, but there's a

compound here. That slide -- sorry. I had read that SEER. I didn't know what that acronym meant. So thank you for showing that, but that was for women above the age of 45.

Now, if the average age of menopause is 51.5, I would like to know how the placebo group did in comparison to women not of that chronological age, but of that number of years from menopause since that's the relevant issue about the change in breast cancer risk.

DR. SACKS: Well, I don't know that I can answer that exactly. I can only tell you that our treatment groups were totally balanced in terms of their age at, you know, menarche menopause and age at first live birth, and the SEER population, we did age adjust it to the women in the SEER group over the age of 45 only.

So that is all that we can do with the available data.

CHAIRMAN BONE: Are there further questions for Dr. Schlesselman?

Dr. Cara, and we'll go around, everybody.

DR. CARA: As a follow-up to Dr. Marcus' question, you said that there was no statistically significant difference between placebo and the

expected incidence based on SEER and IARC data. Was that difference significant for the Xenical treated? Was the difference --

DR. SACKS: Excuse me. I was --

DR. CARA: Let me repeat the question. You said that the difference between the incidence based on SEER and IARC data and the placebo was not statistically significant.

DR. SACKS: No, no. I'm sorry. Maybe you misunderstood what I said. The lowering -- the relative risk in the placebo group is less than one. It is not significantly different from one. That's --

DR. CARA: But is the other --

DR. SACKS: Yes, the confidence interval does -- yes, it is significant.

DR. CARA: So the Xenical treatment is significantly different?

DR. SACKS: Yes, because the confidence interval in that particular comparison does not contain one. That's correct.

CHAIRMAN BONE: Could you put that back up then?

DR. SACKS: Sure. That was L--

DR. CARA: It's in page 102.

DR. SACKS: It's L-5 or L-6, please.

Okay. So the placebo comparison is not different from one, and the orlistat comparison is.

PARTICIPANT: That's in Volume 3, isn't it?

DR. SACKS: Oh, I'm sorry. I think I asked for L-6. Oh, the slide before this one. I'm sorry. L-5. My mistake. Excuse me.

In this situation, again, the placebo comparison is not different from one, and the orlistat comparison is. The same holds in both of these slides.

This is L-5 and L-6. They're both -- okay. L-6 for the trial plus the survey, L-6. Oh, this one isn't. I'm sorry.

For the trial plus the survey period, there is no significant -- none of these comparisons are statistically significantly different from 1.0 relative risk.

DR. CARA: But the confidence interval there is .094.

DR. SACKS: Right.

DR. CARA: Am I reading that?

DR. SACKS: Right. It contains the number one.

DR. CARA: It's awfully close.

DR. SACKS: Oh, I don't disagree with that.

CHAIRMAN BONE: All right. So we've clarified this point, that for the survey period -- for the study period we can see that the placebo group has a relative risk that is less than one, and for the study period the relative risk for the treatment group is 3.6, and that confidence interval excludes one.

If you include the survey period, you have the same observation about the placebo group that's .5 and the confidence interval includes one, and the relative risk for the treatment group, if you include the add-on survey period, remains higher, but the confidence interval now goes as low as 0.84, therefore, including 1.40.

DR. SACKS: Right. It's 1.7, including -- okay.

CHAIRMAN BONE: Okay. Thank you.

I think there may be additional questions along these lines.

DR. SACKS: For me?

CHAIRMAN BONE: Yes. I think there are several questions actually.

DR. SACKS: Okay. I'll try to answer them.

CHAIRMAN BONE: I think Dr. Siegel had a question. Everybody is going to get their chance.

Can we turn on Dr. Siegel's microphone, please?

DR. SIEGEL: No, it was on.

You made the case for it not being an initiator, but I was trying to follow your rationale for this thing not possibly being a stimulator, and you had mentioned that if it were a stimulator, you would expect more breast cancers early in the study period, when in fact, you know, if you're starting out with small tumors perhaps you would expect them later.

I just want to understand what you were saying.

DR. SCHLESSELMAN: If it were a stimulator, one would, indeed, expect more tumors early in the study. I also expressed the view that if it were a stimulator, one would expect the excess number of breast cancers to have continued into the survey period.

So to me the decline in relative risk with continued follow-up is not consistent with my expectation. So, for example, women who use hormone replacement therapy long term are at about 30 percent increased risk of breast cancer, relative risk of 1.3.

When HRT is stopped and you look at risk of breast cancer in women who have previously used HRT, you will not find relative risk immediately dropping to 1.0. It is the excess cases of breast cancer continue beyond the period of stimulation, if you want to say.

CHAIRMAN BONE: But, by the same token, the apparent excess rate of breast cancer doesn't appear for several years. It's not an early effect at all in patients on hormone replacement therapy.

DR. SCHLESSELMAN: True.

CHAIRMAN BONE: Okay. I think that's the point Dr. Siegel was going to, is that the idea that a stimulator would necessarily produce an early effect isn't borne out at least by that experience.

DR. SCHLESSELMAN: Well, if that's the case, then you have to explain why does the excess occur early on in the study if you're going to be using cause-effect as your explanation.

CHAIRMAN BONE: Okay. Well, I guess the point may be that we can't a priori say how that would work without knowing the mechanism of action.

DR. SCHLESSELMAN: Agreed.

CHAIRMAN BONE: Okay. Dr. Molitch.

DR. MOLITCH: My guess is that this afternoon we're going to keep coming back to this

estrogen question as the possible mediator of cause and effect, if there is one at all. I'm sort of intrigued by Dr. Marcus' observation that menopauses four or five years earlier than the population is expected to be, and also that means that perhaps if they were started on hormone replacement at menopause, that they, therefore, have been on hormone replacement for a good four to five years, longer perhaps than others might be.

And hormone replacement at 50 to 60 percent is also a much higher percentage of women that accept hormone replacement than in the population at large as well. So it's an intriguing type of thing.

On the other hand, if you take the comparison, the SEER group, I suspect, with much lower rates of hormone replacement, it may actually help the statistics rather than hurt the statistics.

CHAIRMAN BONE: Let's see. I think Dr. Davidson and Dr. Hirsch. Everyone will get -- yes.

DR. DAVIDSON: You know, if I see the data and I look at relative risk, you know, at any point with any way that the data is, you know, given to us, there's still a three times higher risk at any time. Am I correct, in any of the studies that were presented?

DR. SCHLESSELMAN: The rates increased. Agreed. The question is why is it increasing, and that is the issue, I believe, why we're here this morning.

DR. DAVIDSON: No, I know, but no matter how we massage the data, it's still three times minimum increased rates; is that correct?

DR. SCHLESSELMAN: That's right.

DR. DAVIDSON: Thank you.

DR. SCHLESSELMAN: For the orlistat, 120 milligram

CHAIRMAN BONE: Right, and let's see. Dr. Critchlow and Dr. New. Everybody, we've got lots of questions here, and we're going to try to mainly stay with Point 3, and we'll get into general discussion in the afternoon.

DR. CRITCHLOW: One comment and a question. Clearly the comparison of the breast cancer incidence and the SEER and IARC data would suggest that obesity in this case is not a risk factor for breast cancer. There's clearly no indication that the placebo group was the same as the SEER/IARC expected rate. So I mean, in my mind one would rule out obesity as a risk factor.

Another thing is given the breadth of the

confidence intervals, I mean, clearly you've got .8 to something very large with 11 cases overall. So the question is not only why are we observing what we're observing here, but what's going to happen when it's out in thousands times the number of exposures that we're seeing here.

And the last is even though these numbers are small and it's probably in our briefing document, but what is the experience of the breast cancer incidence among those on the two-year exposure versus one year exposure?

DR. SACKS: I don't have the data cut that way. What we have is person-years of follow-up on 120. So what you're seeing is if a person was on 120 for one year, they were counted at the one year or two year.

DR. CRITCHLOW: I'm just trying to get a little bit at the question of --

DR. SACKS: I don't have that. I'm sorry.

CHAIRMAN BONE: Can you get it?

DR. CRITCHLOW: I mean, if we're talking about possible promotor effect or stimulation, if there's any evidence at all.

CHAIRMAN BONE: Obviously you have the data to make those calculations. It's a question of

whether you can do them today.

DR. SCHLESSELMAN: May I comment on two of the remarks that were made?

With regard to obesity being a risk factor for breast cancer, I wouldn't make a conclusion based on the comparison from this clinical trial with the SEER and IARC data. I did not present these. I think that the best comparisons with regard to addressing the issue of orlistat is the internal control that was designed as part of --

DR. CRITCHLOW: No, I completely agree with that.

DR. SCHLESSELMAN: -- the, quote, human experiment.

With regard to the question about what will occur with wider distribution of use of the drug, the honest answer is we don't know. I gain some reassurance with the fact that further follow-up through the survey we saw a decline in relative risk rather than an increase in relative risk, which I would have expected.

DR. CRITCHLOW: Right, but the exposure was -- I mean there was no longer any exposure.

CHAIRMAN BONE: Dr. New, then Dr. Ellis, and Dr. Hirsch.

DR. NEW: May I ask you what figure you're using for the increased risk of women who take hormone replacement therapy after menopause? The CDC figure which was recently released is that the risk is increased by 30 percent, and that's confounded by the fact that 60 percent of your women are taking it.

Can you sort of give me some idea of how you mitigate those two figures?

DR. SCHLESSELMAN: The 30 percent increase? That was reported by a meta analysis. I don't have the citation right at hand.

DR. NEW: Yes, but I'm saying since anyone taking hormone replacement therapy already has an increased risk of 30 percent, and 60 percent of the women that you're studying are taking hormone replacement therapy or approximately 60 percent, have you calculated that into the probability of orlistat being an inciting agent?

DR. SCHLESSELMAN: Whether orlistat in combination with HRT --

DR. NEW: Yeah.

DR. SCHLESSELMAN: -- might have some effect?

DR. NEW: Yes.

DR. SCHLESSELMAN: This was a randomized

trial, and so since the women, whether they're on HRT or not, are being assigned at random to placebo, to orlistat 30/60, to orlistat 120, since the assignment is at random, one would not expect that all of the women on HRT would end up in the orlistat 120, so that just as we did not find that all women with a family history of breast cancer in a mother ended up in 120.

The question that you're asking about a specific interaction between --

DR. NEW: Yes.

DR. SCHLESSELMAN: -- HRTs and orlistat 120, I'm not capable to answer. I don't know whether there's anyone that can address it.

DR. NEW: Just pursuant to that, can I ask you: did you measure serum estradiol levels on people taking orlistat?

DR. HUBER: We did, but if you want, I guess we can go ahead with that. I mean we've had that question multiple times, Mr. Chair. Should we go ahead and show the data now or wait till that comes up in the presentation?

CHAIRMAN BONE: I think there's several people on the Committee who would like to have that now. It might get is forward.

DR. HUBER: Can I answer with --

CHAIRMAN BONE: That will shorten the subsequent presentation to that extent.

DR. HUBER: Okay. I guess the first question also is with regards to the HRT in patients, we actually looked at how many of the actual breast cancer cases occurred on HRT, and do we have that slide? We'll get that for you in just a second, how many of the actual patients.

Okay. Slide on.

Okay. What this shows for you is these are all the patients broken down by whether they were on orlistat 120, 60 and placebo, and this is the day of diagnosis. This is kind of the point of reference in the future for all the slides. That's kind of our identifier, and then this is whether or not they're on HRT.

As you can see here, one, two, three, four, and then there were two of the cases that came in the follow-up that we didn't have the information on.

CHAIRMAN BONE: Thank you.

DR. HUBER: So I guess we need the main presentation. Actually can I back up one?

Okay. In order to look at this, I think the thing that is important is we did not

prospectively plan to assess estrogen levels in these studies because we did not feel that this was an issue going in.

So once this became an issue and repeatedly questions were raised about the effect on estrogen, we sought a way to retrospectively evaluate this, and what we've identified for you is a total of 77 patients, 32 on placebo and 45 that received orlistat 120.

In order to obtain this data, we targeted women who were at least 45 years of age, as this was the target population, and to make sure they were post menopausal, that they had an FSH over 30. That was the cut we identified.

The reason we wanted to look at post menopausal is several technical concerns were raised that premenopausal women not doing this prospectively, it would be very difficult to assess the value of the data.

So what we did is then the other thing is they had to have adequate sample volume. We were trying to retrieve archive samples. So if they had sufficient volume at baseline and at six months and they met these criteria, we included them in the study, and I believe it was the U.S. trials for this

because that was the place where we had access to the information.

So if you look at this, on these patients, they had a median age 55 and 58. The BMI was 35.7 to 35.5 at baseline, and what I think is important to note is that if you look at weight loss, the mean weight loss, and this is kilograms from baseline, was minus two and minus 6.2. So what's important to note is that this population, the orlistat group, did have a greater weight loss, which would be consistent with the trial population.

Now, these are the plasma estradiol levels, and this is, once again, the women who are at least 45 years whose FSH was greater than 30. In nanograms per deciliter what we have here is the mean value at day one and then at six months within the 32 patients, and this is the standard error here.

As you can see, there was not a significant change. There was a slight change in placebo and orlistat, but what is important to note is that the change actually was greater in placebo, if anything. The orlistat really showed no significant change.

Then perhaps more importantly, we looked at plasma estrone levels, and this is looking at this

once again day one to day 169, and really there's no change in estrone exposure.

And then finally to make sure we got confounding effects of sex hormone binding globulin we can look here, and once again there's really no major changes here, and in fact, they go up, which should decrease the estrogen exposure.

So I think based on this data we felt there was no evidence of a substantial increase in estrogen exposure that could account for the observed imbalance.

CHAIRMAN BONE: Why would the sex hormone binding globulin levels go up? Do you think that's meaningful?

DR. HUBER: It's a very small -- yes.

DR. HAUPTMAN: You expect them to go up as you lose weight.

CHAIRMAN BONE: All right. Maybe.

DR. MOLITCH: So these are women on or off estrogen replacement therapy? I'm sorry.

CHAIRMAN BONE: Yes. Could you show the sex hormone binding globulin data again?

DR. HUBER: Okay. Sex hormone binding globulin data?

CHAIRMAN BONE: Yes.

DR. HUBER: Okay. There you go.

DR. MARCUS: I need to ask a point of clarification. Go back to your estradiol slide, please. It looks like you're in nanograms per DL. So those are picagrams per mL. You're talking about levels per ten picagrams per milliliter. Did you use an assay that is sensitive down to two picagrams per mL or did you have -- was it the traditional commercial assays which have a cutoff at five?

And then if so, how did you record people who were undetectable? Some studies would show 30 percent or more of women post menopausal with the usual commercial assays are undetectable.

DR. CANOVATCHEL; I'm Dr. Bill Canovatchel, International Clinical Research.

These assays were performed by Endocrine Sciences, which is a well recognized laboratory for doing high quality assays.

CHAIRMAN BONE: Do you know what assay technique they used?

DR. HUBER: I guess we can track it down here.

CHAIRMAN BONE: I think DR. Marcus just wants an answer to his question.

DR. HUBER: I'm sorry. It's just taking

a little while to get the methodology.

For estradiol specifically was a radioamino assay after extraction and LH-20 chromatography based on the method of Wu and Lundy

DR. MARCUS: Do they say what the sensitivity of the assay was?

DR. HUBER: Yes, .5 nanograms per deciliter.

DR. MARCUS: Thank you, thank you.

CHAIRMAN BONE: Point, five. So that's five picagrams per milliliter.

DR. HUBER: Yeah.

CHAIRMAN BONE: Thank you.

Let's see. Now I'm trying to remember the order. Dr. Ellis, I think, has been and then Dr. Hirsch are the two questioners with the greatest tenure as waiting their turn.

(Laughter.)

DR. ELLIS: Since I don't have tenure at my university, I'm not sure that means that much.

CHAIRMAN BONE: We just granted it here.

DR. ELLIS: I have a question with respect to the endocrinology. As we know, in post menopausal women the origin of the estrogens is through the action of aromatase (phonetic) and the substrate for

aromatase is androgenic precursors. I was wondering whether you looked at the androgenic precursors.

DR. HAUPTMAN: No, we didn't. We had only a small amount of sample left. So we did the ones that we thought would be the most pertinent, but certainly, as you know, most of the estradiol comes from the estrone, which comes from aromadization, and as they lost weight you would expect to see changes as well.

DR. ELLIS: My second and my original question, we may want to address this later. It comes to the issue of detection bias, and I was wondering about morphometric analysis in women who lose weight, and in particular whether you asked any questions concerning change in breast size, for example, change in the brazier size or any information as to whether the weight loss is associated with physical changes in breasts.

DR. HUBER: No, no.

DR. ELLIS: Thank you.

CHAIRMAN BONE: I think Dr. Hirsch.

DR. HIRSCH: Yes. I had two questions, one for Dr. Schlesselman.

Could you tell us, Dr. Schlesselman -- you were good enough to show us the timing in a linear way

of when these nine cases occurred in the treatment group. What is your best estimate on your expert knowledge of this area as to the number of these that would have been present before Xenical was given, that is, that occurred -- the breast malignancy began before administration of drug?

DR. SCHLESSELMAN: You're going to hear later from the pathologists a pathologic assessment of this issue. I think honestly I don't know. Part of the problem has to do with whether these women had been under mammographic screening before they entered the trial or whether when they started the study a more intense medical care experience occurred, in which case one would expect, say, existing tumors to be detected, say, by what is called a prevalence screen.

CHAIRMAN BONE: Thank you.

DR. HIRSCH: But I have question Part B then, which is the biostatistical one. So perhaps your associate can help with this.

It's the following. Undoubtedly the case can be made that many of these tumors were present before. I know you're not at this moment prepared to give a number, but I'm sure we'll hear that.

Now, that has very profound biostatistical

consequences, I would think, and I'd like to know how you handle that. Namely, it means that for whatever reason and unbeknownst to you, you dealt with two very different groups in these two patients, the placebo versus the treatment vis-a-vis having had or having begun a malignancy.

To remove susceptibles, as it were, from the treatment group, susceptibles to Xenical if such exist, if you see what I mean, is a marked problem of randomization that you couldn't have known about, but nevertheless in retrospect is present, namely, there were many more people who began Xenical treatment having malignancies than who began placebo treatment.

DR. SACKS: Right.

DR. HIRSCH: And that being the case, that's a very profound lack of randomization, although no one's fault. I understand, but nevertheless, in retrospect you may have removed any susceptibles who might have been affected by Xenical treatment, if you follow my logic. I hope you do because it is an important point.

DR. SACKS: Go ahead.

DR. SCHLESSELMAN: As I understand things, there was no prescreening to exclude women from the trials so that the only removal of women, quote, at

risk for breast cancer was for those who developed it, and they're counted in the statistics.

So all women in this trial were at risk of breast cancer. Some as you'll hear later had it at the time they were enrolled in the study, but there are two issues with regard to cause-effect, and that is whether a compound can initiate a tumor or when a tumor is present whether it can stimulate the growth of the tumor.

DR. HIRSCH: No, I understand fully what you're saying. I'm just saying that in retrospect it turns out that the risk for cancer was much greater in the group who received drug, unbeknownst to you, as evidenced by the fact that they had many more tumors before beginning. That means that vis-a-vis the Xenical tumor connection, if there is such, you have a very badly designed study for its detection.

DR. SACKS: Well, I should say these were obesity trials, and we didn't expect to see this, but if I could quote, and I don't have his report right in front of me, but in Dr. Rothman's report, one of his comments is that these cases would have occurred, in his opinion, no matter which group the women had been randomized to, which, I mean, this is the way --

CHAIRMAN BONE: Right.

DR. SACKS: But I wanted to get back to the question I had been asked about did we have the rates for the two year and the one year, and actually in the FDA statistician's report, there is a table that I think addresses your question.

Okay. Thank you.

CHAIRMAN BONE: I'm sure we'll get to that.

Further questions about Dr. Schlesselman's presentation, please?

Dr. Cara, and then are there any others after that?

DR. CARA: If I interpreted one of your slides correctly, you suggested that one way to get a better sense of the true incidence of breast cancer was by excluding those patients that had been diagnosed as having breast cancer within the first six months of therapy, and I believe that number came to a total of six patients; is that correct?

Did you do a relative risk assessment of the remaining patients compared to placebo? And if so, what is the relative risk?

DR. SCHLESSELMAN: Yes, we need to go back to the slides in the presentation I made that address this issue. The first is Q-11.

DR. CARA: I've got it.

CHAIRMAN BONE: Okay. That's done. Thank you. Dr. Cara has looked at the paper handout and refreshed his memory.

Are there any further questions for Dr. Schlesselman before we go on to the next? Oh, I'm sorry. Excuse me. Dr. Simon, yes.

DR. SIMON: You've presented an analysis based on patient years at risk and given confidence intervals for relative risks, and your results don't exactly agree with two other analyses that were done, one that was done by the FDA not based on patient-years of risk, but based just upon how many breast cancers were observed in how many patients in each of the groups.

And the FDA report also alludes to a P value of .07 that was computed presumably, I believe, by the company based on a log rank analysis of time to detection of the breast cancer cases. Do you have any comment on the fact that -- I mean, you have made a presentation claiming that these results are not statistically significant, but that's sort of in conflict certainly with the FDA analysis based on like a Fisher's exact test, just on number of cases out of number of patients, and somewhat in conflict with the

log rank analysis with time to event.

DR. SCHLESSELMAN: If you turn to the FDA's analysis, you will see that, firstly, their estimates of relative risk based on OS (phonetic) ratios are slightly higher than the rate ratios that I presented here, with one exception, with one exception. The confidence intervals on the OS ratios in the FDA's analysis cover 1.0.

The P values are small in the FDA's analysis. I think that no one would dispute the fact that what we have is an unusual occurrence. The question is why.

CHAIRMAN BONE: All right. Thank you.

We'll proceed with the next presentation, which I believe will be Dr. Anderson.

Just for planning purposes, I think we'll probably take our break after the sponsor presentation for the lunchtime, but we'll obviously be having a shortened lunch.

DR. ANDERSON: Good morning. My name is Tim Anderson. I'm Director of Toxicology and Pathology at Hoffman-LaRoche, and the purpose of my presentation today is to present an overview of the preclinical data that is relevant to us understanding the clinical significance of the detected breast

tumors.

Any drug that is intended for long term human use requires an evaluation of its carcinogenic potential. This is done by conducting several short term genotoxicity assays and by conducting two two-year carcinogenicity studies in mice and rats.

The results of these studies showed that orlistat has no carcinogenic potential. When a question arose regarding breast cancer in the clinical trials, we thought it was necessary to reevaluate the preclinical data to determine the true clinical relevance of the clinical detections.

The preclinical animal studies are relevant to our discussion here today because it is unknown for an agent which causes or stimulates tumors in humans; it is unknown for an agent that causes tumors or stimulates tumors in humans to do that without also causing similar effects in rodents. In fact, of the 19 pharmaceuticals that are classified as human carcinogens, all of them cause similar effects in rodents.

This is from the database of the International Agency for Research on Cancer, a division of WHO.

All genotoxicity and carcinogenicity

studies done with orlistat were done according to internationally accepted guidelines and have been reviewed and accepted by the FDA.

This slide shows the battery of tests that we conducted with orlistat in both bacterial and mammalian cells, in both in vivo and in vitro assays, and testing both orlistat and its metabolites.

All studies were negative. This is important in our assessment because it tells us that orlistat does not have properties of a genotoxic carcinogen.

The data on this slide shows that the animal studies done with orlistat are suitable to assess carcinogenic risk of orlistat because they show high exposure to orlistat and its two metabolites over one to two years of treatment.

For example, I draw your attention to the rat carcinogenicity study. This data show that for two years at the high dose of 1,000 milligrams per kilogram, the rat had 730 times the blood level of orlistat as would be expected at the human use dose of 120.

The rat also has a high spontaneous background incidence of mammary tumors. This culmination of the high systemic exposure to orlistat

and its metabolites, combined with a high background incidence of mammary tumors in the rat, makes this model particularly relevant to our discussion today.

On this slide you can see the design of the carcinogenicity study and the results. Let me draw your attention to the design. You can see we have two control groups and the doses of orlistat.

We require two control groups in all of our carcinogenicity studies because it is very common due to biologic variability or chance to have either an increase or decrease of spontaneously occurring tumors.

There are two points that I can make from this slide. One, clearly there is no increase in either mammary adenomas or mammary carcinomas.

Second, there is actually a decrease in the incidence of mammary fibroadenomas, which was statistically significant.

This is data from the mouse carcinogenicity study with orlistat. Again, you see the two control groups, the four doses of orlistat. The conclusion from this slide is clearly there is no increase in incidence of mammary adenocarcinomas. As you can see, five of 99 animals and only one orlistat treated animal had mammary tumors.

Thus, at this point we can see that there's no evidence for genotoxic activity with orlistat. We can also see that in two two-year animal carcinogenicity studies that orlistat did not initiate or promote tumors of any type, particularly in the mammary gland.

We've also seen that those carcinogenicity studies were suitable to assess carcinogenic risk because they were exposed to much higher levels of orlistat and its two metabolites over the lifetime of the animals than humans see at the clinically used dose.

We next addressed the potential stimulatory effects of orlistat. What we were able to do with the thorough reevaluation of our animal studies was look for effects of orlistat upon stimulation of mammary gland, upon stimulation of mammary tumors, and because hormones are known stimulators of human tumor growth, we could look for evidence of hormonal effects in our animal studies.

This is data from the same rat study that I showed you previously in which we saw the high systemic exposure to orlistat and its two metabolites, and we saw the decreased incidence of mammary fibroadenomas.

Again, as I mentioned previously that study is particular relevant to our discussion today in assessing growth promotion properties of orlistat on mammary tumors because the rat has a high spontaneous background incidence of mammary tumors. In this case we see 17 of 50 and 20 of 50 rats had palpable masses on the chest and abdomen which histologically correlated to mammary tumors.

The data on this slide show us that we detected the number of masses and time to detection, and an important point I want to make is that the clinical palpation of these palpable mammary masses is the animal correlate to the clinical detection of human breast tumors by palpation.

We see that there's a decreased incidence of palpable masses which correlates with a decrease in mammary tumors. We also see that there is no change in time to detection between control and treated orlistat groups.

The conclusion from this data is that there's no evidence that orlistat stimulates the growth of rodent mammary tumors.

We were also able to evaluate to see if orlistat caused hormonal effects in animal studies by the histopathologic assessment of morphologic changes

in hormone responsive tissues. We saw no changes in mammary tissue, testes, ovaries, vagina, or uterus in mice, rats, or dogs treated at high levels of orlistat for one to two years.

Because morphologic changes in hormone responsive tissues are sensitive indicators of hormonal status, we can conclude that in these studies there's no indication, no evidence for hormonal activity by orlistat.

We were also able to assess physiological or functional hormonal changes by looking at the repro. toxicity studies. In these studies we saw no changes in fertility, reproductive performance, teratogenicity, or perinatal effects in rats.

Thus, the combination of the lack of morphologic effects and the lack of functional hormonal effects leads us to conclude that there's no evidence that orlistat induces changes in estrogen, progesterone, or any other hormonal activity.

In addition to our reevaluation of the animal toxicity studies, we asked Dr. Gary Williams of the American Health Foundation also to reevaluate our studies as an outside expert. Dr. Williams concluded that the nonclinical studies of orlistat provide no findings to suggest any human cancer hazard, and in

particular, any potential for enhancing or accelerating breast cancer development.

Dr. Williams is with us today to address any questions the panel may have.

In conclusion, the overall evaluation of our preclinical studies shows that orlistat has no evidence of carcinogenic potential in animals. The evidence is such that the systemic exposure to orlistat and its metabolites is much higher in animals than in human.

There is no evidence for genotoxic activity with orlistat. There was no increased incidence of mammary adenomas, nor carcinomas in rodents. There was a decreased incidence of mammary fibroadenomas in the rat study, and there is no evidence of carcinogenicity at any other site in rats or mice.

We also saw no evidence of hormonal activity in the toxicity or the repro. toxicity studies. We saw no evidence of growth stimulation of normal mammary tissue in three species treated for one to two years with orlistat, and very importantly, we saw no growth enhancement of spontaneously occurring rodent mammary tumors.

Thus, overall there is nothing in the

preclinical data that suggests orlistat has any carcinogenic or stimulatory effect upon the mammary gland, nor any other tissue. In the absence of these animal findings, we would not expect to see those findings in humans.

Now I think it's relevant that we look at the clinical data, and Dr. Huber will present an overview of that next.

CHAIRMAN BONE: All right. I think there will be several questions for Dr. Anderson, and I may just start, if I might.

Dr. Anderson, how was the drug administered in the carcinogenicity studies?

DR. ANDERSON: The drug in the carcinogenicity studies was mixed in the powdered diet of the mice and rats and given ad libitum in the diet, and then as their body weight changed, we changed the concentration of orlistat so that they would get the proper dose.

CHAIRMAN BONE: I see, and what's the fat content of that dietary powder?

DR. ANDERSON: We actually gave the rodents a higher fat diet than normal rodent diet would be.

CHAIRMAN BONE: Yeah.

DR. ANDERSON: And I believe that fat as a percentage of calories was 20 percent.

CHAIRMAN BONE: I see. I guess I have a further question, and that is what you've demonstrated is the experiments that you conducted did not demonstrate carcinogenic mechanism, and this is based on the idea that the carcinogenic mechanism would be related to the systemic effects of the drug, but actually the mechanism of action of the drug in humans is to cause malabsorption of fat, and we're aware from all of the discussion that many other substances, probably the majority of which are not even identified, are malabsorbed along with the fat.

Now, is there anything about your experiments which would address the question of a human dietary constituent that had an anti-tumor growth effect of some kind being malabsorbed?

DR. ANDERSON: You're perfectly right in what the animal studies can tell us is the effects of high systemic exposure to orlistat and metabolites. What the animal studies can additionally tell us is that when you bracket the appropriate human pharmacodynamic dose and have approximately the same percent lipase inhibition, that you also do not see direct or indirect effects.

What the animal studies cannot tell us though is what effects you would see with orlistat and a human diet. I think that's dependent on the clinical data.

CHAIRMAN BONE: So if that's the mechanism, then it's a different one than the one you were kind of -- the kind of mechanism that we would normally investigate and that you've investigated.

DR. ANDERSON: I think the animal studies will tell you if there is an initiation, promotion or stimulation of effect due to orlistat. It will not tell you the effects of a human diet.

CHAIRMAN BONE: Thank you.

Dr. Molitch had questions and several others, I'm sure.

DR. MOLITCH: I'm certainly not expert in these types of studies. I just want to be reassured that when you start at such a high multiple of the daily dose and exposure that you may not miss something with earlier or smaller amounts. We certainly know that with radiation, for example, that a very small amount of radiation may be carcinogenic where a large amount may be therapeutic, and I just want to be reassured that that kind of thing couldn't happen with these types of potential carcinogens.

DR. ANDERSON: The way we address that is, of course, we have a variety of doses, three and four doses, and we can see that the exposure at the low doses is proportional to the dose or at least there's a much lower systemic exposure.

DR. MOLITCH: But even the low dose is 50 times the human dose. I mean do you have like something once or twice times the human dose?

I mean you probably have done this with the regular pharmacokinetics. Have those rats also been followed up for two years?

DR. ANDERSON: I'm sorry, sir. Could you readdress your question?

DR. MOLITCH: I mean something that would approximate the normal human dose that you would give, have those rats also been followed up for two years to make sure that they don't cause tumors?

DR. ANDERSON: Could I have the primary slide number five, please?

Part of the design of the carcinogenicity studies is reviewed with the FDA Carcinogenicity Assessment Committee, and we required their review and approval of doses and exposures before we continued. So the dose level so that we get adequate systemic exposure was agreed with the Carcinogenicity Advisory

Committee.

However, despite having to go to high oral doses to get high exposure, in the mouse study -- could I have the slide please? This is the rat study. Could I have the next one, please? -- you see we have four doses here. The lower dose of 25 milligrams per day is the approximate bracketing to human pharmacodynamic dose. So we added that lower dose so that we could not only see high systemic effects, but also pharmacodynamic effects of similar lipase inhibition as in humans.

DR. MOLITCH: Thank you.

DR. ANDERSON: You're welcome.

CHAIRMAN BONE: One hundred and twenty milligrams t.i.d. would be 360 milligrams per day, which would be about five milligrams per kilogram per day. So that's actually about a fivefold; is that right?

DR. ANDERSON: You know, the best person to answer that is Dr. Kamm, who has been with orlistat for the ten years we've been studying that.

CHAIRMAN BONE: Well, it's just arithmetic really.

DR. KAMM: In terms of -- Jerry Kamm, Department of Toxicology and Pathology.

The low dose in the mouse study was -- let me say something first about systemic exposure in animals. In all of the animal studies that we've done when the doses are approximately 70 to 100 milligrams per kilogram or less, orlistat and its metabolites are undetectable in the plasma, which approximates the situation that you see clinically at 120 milligrams per kilogram.

The orlistat was undetectable in the plasma of mice that received 25 milligrams per kilogram for two years.

Have I addressed the question?

CHAIRMAN BONE: No. I think we're just trying to see if a comparable dose was given.

DR. KAMM: Yes.

CHAIRMAN BONE: And the dose per day in the 120 milligrams t.i.d. is 360 milligrams. For the subjects in the study here where we have 100 milligrams -- 100 kilograms --

DR. KAMM: Right.

CHAIRMAN BONE: -- that would be 3.6 --

DR. KAMM: Well, no, it would be --

CHAIRMAN BONE: -- milligrams per kilogram per day.

DR. KAMM: Right.

CHAIRMAN BONE: Which is one-eighth of this exposure approximately.

DR. KAMM: That's correct.

CHAIRMAN BONE: Okay. That's the point.

DR. ANDERSON: But if I could additionally clarify that, that low dose in the mouse carcinogenicity study is equivalent to about 30 percent inhibition of fat absorption, which is similar to humans.

CHAIRMAN BONE: I see. So physiologically it has -- you said it would be pharmacodynamically comparable. I see your point.

DR. ANDERSON: I was referring to pharmacodynamic percent of lipase inhibition in the intestine.

CHAIRMAN BONE: Thank you very much. That's very clarifying.

DR. ANDERSON: And we added that low dose to cover the physiology.

CHAIRMAN BONE: Very helpful point.

Okay. Now, who's next? On the program the next speaker is Dr. McGee.

DR. HUBER: I think we're going to shorten it if it's okay.

CHAIRMAN BONE: Suit yourself, and I would

like to introduce Dr. McGee to present the pathology of the tumors.

Thank you.

DR. McGEE: Good morning. I would just simply like to reiterate that I don't look at all like Dr. Huber, and I'm sure my accent is completely unfamiliar in the sense that I am not American.

(Laughter.)

DR. McGEE: My credentials -- as Dr. Huber is -- my credentials are shown on this first slide here. My name is Jim McGee. I am the Chairman of Pathology and Bacteriology in the University of Oxford.

Some one asked me the same question this morning, was that the same as Oxford University, and the answer is yes.

(Laughter.)

DR. McGEE: It's simply differences in the way we use English on both sides of the Atlantic.

To be serious for a moment, however, and for the rest of this presentation, I have to declare also that I do not own any Roche stock, nor do I have any commercial interest in orlistat.

I was asked to come into this problem last August, August '97, and the reason that I was asked to

come into it is because of these two asterisks that you see at the bottom.

The first is that my prime research interest is in the molecular pathology of breast cancer and particularly chromosome 11Q. However, in the present context, the more important thing is that I'm a member of this committee listed at the bottom, namely, the U.K. National Coordinating Committee on Breast Cancer pathology.

Now, the "raison d'etre" of this group is to work out and implement the laboratory diagnostic criteria and guidelines for the diagnosis of breast disease not only in the everyday clinic, but also in external quality assurance programs.

Now, it is quite important for you to realize that in the U.K. you are not allowed to make a diagnosis of breast cancer or, in fact, to participate in a breast screening program unless you have called a designated pathologist and have participated in this external quality assurance program.

It has been quite successful in the U.K. It has been adopted and has now been adopted by a number of countries in the European Union and Australia and Singapore, et cetera.

Now, you're all aware of the problem and my involvement herein is summarized here on this slide.

In that there is an imbalance, and this is the issue before us today, between the number of cancers that exist in the placebo group and also in the orlistat group of the trial, and so that you don't have to do any arithmetic, for those of you who don't have the enormous volumes in front of you, there were, in fact, three cases in the placebo group and 11 or say 12 in the orlistat group.

Now, I want to break these issues down into two, and the first issue as I have identified it is as shown on this transparency here, and I'm afraid the batteries on my thing have gone again. I can work without it.

The question really here under Issue 1 is: does orlistat cause breast cancer? I think that's the first question that we have to address.

The second question is: does orlistat enhance the growth of a preexisting cancer? And I'm going to address both of these topics completely independently.

On Issue No. 1, what I'm going to do is I'm going to present evidence indicating that orlistat

is not causally related to breast cancer either as an initiator or promoter, and I apologize for the typo in the bottom line.

The evidence on which that is based I will come to in a moment. However, I think it's important you should know what the criteria were that I used in the study, and the first thing to point out which I regarded as probably the most important thing in the beginning of the study was that I was complete blinded. Now, that was my choice. It was not the choice of anyone else.

I did not want to see the primary reports of the pathologists concerned. I did not want to see any of the volumes of data which had been provided to me by Hoffman-LaRoche lest I be biased in knowing which patients were on orlistat and those that were not. So I simply analyzed them in that way.

The second thing was I then analyzed all of the microscopic slides from all cases, and this was quite a large task because those cases were located in the United States and the various other countries identified there in Europe,a nd that meant getting on and off lots and lots of planes, which was not a very pleasant experience, but I take this problem very seriously.

I point out in the third bullet that remarkably, and I do mean remarkably, that I was able to retrieve or was given every slide from every patient who had developed cancer, and any of you who have been involved in cancer registries will realize how difficult that is.

Then finally, when I had done my analysis and come to the conclusions on the basis of the histopathology, I then became unblinded, looked at the primary pathologist's report and all of the other data, and my report, which integrates my views and the information provided by others, is in Volume 2 of the document in front of you.

Now, because pathology is a rather special discipline, as all of our disciplines are -- I'm sorry. Here we go. Okay. That's better -- I thought it was important here to define some histopathologic term. "Histopathological" is the way we would say it on the other side of the Atlantic. So if I use that rather than "histopathologic," please understand me.

The breast, as you know, is made to lactate and produce milk, and in the center of the breast what you have is a duct system leading up to the nipple which produces that or the channel along which that milk is delivered.

That very large duct known as the lactiferous duct arborizes like a tree all the way down into these little lobular units, and it's the lobular units that produce milk.

Now, the thing I want you to focus on in view of the terminology issue is that on your left where I've magnified these lobular units, and it's composed of two things. It's composed of a central area known as the acinus where the milk is produced, and then that little duct that goes into this, this end.

Now, all cancers or virtually all cancers of the breast occur in this area, and as far as terminology is concerned, I will use the word "lobular" and this refers to invasive cancers that arise in the milk producing part, namely, the acinus, and I will use the term "LCIS," which is the lobular carcinoma in situ, and that refers to an in situ lesion arising in that area.

I will also use the term "ductile cancer," "invasive ductile cancer of the breast," and they arise in the little duct going into the acinus.

I will also use the term "DCIS." DCIS simply means ductile carcinoma in situ, and then finally if I use the genetic term CIS, that's me

grouping them both together.

All right. Now, what criteria did I use in doing the study to determine whether, in fact, there was a causal relationship between orlistat and the development of breast tumors?

Well, the first thing that I looked for was carcinoma in situ, that is, a combination or I'm using the generic term CIS, namely, LCIS and DCIS, and this is a lesion, a local carcinoma in situ. It isn't really cancer. It is a precursor of cancer which occurs in a very large number of the population in the breast screening program in the U.K. It occurs in about 20 percent of 1,000 women screened.

It exists, and when it goes on to develop or progress into invasive cancer, it does so only in 25 percent of women, and additionally, it takes 20 to 30 years to do that. So if you find CIS, carcinoma in situ, in a breast, what that tells you is that a precursor lesion, which increases the risk factor by a factor of ten at least, that has been present for a very long time.

The second group of criteria that I used was tumor classification. Now, these tell you separate things. The first thing that it tells you is that if you truly believe that a compound causes

breast cancer, what you would expect to find is that the tumor type would be homogeneous. It is not.

The second thing you would expect is that the grade of the tumor, that is, the proliferation rate and the differentiation within the tumor, would also be uniform, and the answer is that it isn't.

The penultimate criteria on this slide is the presence of lymph node metastasis. Now, what lymph node metastasis tells you is not only has the tumor spread, but it's generally accepted in the clinic -- and I do actually work in the clinic, although I'm the Chairman of a department in Oxford University -- that that tumor has been around for some time and usually years.

And then finally, you can calculate tumor size and from that you can actually determine whether the tumor was present at randomization or before.

All right. Now tumor size. I divided this into two. The first thing to realize is that it takes a breast cancer nine to 17 years to grow from one cell to a clinically detectable one, such as ten millimeters, and it does that go undergoing 30 volume doubling times.

Now, I'm not going to get into fancy mathematics because I'm not a mathematician, but

simplifying that, what that simply tells you there is that if you double the diameter of a sphere which is a tumor, what you actually do is you increase the number of tumor cells within that sphere by a factor of eight, and that's very important.

How do you do these calculations? Well, there's a number of ways in which you can do it, but the method I've chosen to use is this one, which is published by Peers. Now, the reason for choosing this is quite simple, and that is that the formula in that publication is based entirely on clinical data. It is not based on cells growing in culture. It is based on the size of tumors measured mammographically in patients in the Dutch breast screening program which has been going on since in the late '80s.

And from that publication the median time for tumor volume doubling is 157 days with confidence limits extending from 121 up to 204. There are other ways of doing it, but I've explained the reasons for me doing it this way.

All right. Now, the next slide is inordinately or was inordinately complicated until last evening, and I hope that I can go through this slowly and methodically with you.

This slide is not incomplete. I'm going

to add a column as we go along. The first column indicates those patients who were in the placebo or the orlistat part of the trial.

The second column indicates the day of diagnosis of the tumor. Now, the day of diagnosis actually tells you quite a lot about the tumor because this is all in the volumes you have in front of you, and if you look at the very last page of my report, which is in Volume 2, if you can't see this screen very well, you will actually see these numbers.

But what I will say here is that this tells you that some of these tumors, it's virtually impossible that it could have arisen as a causal effect of orlistat because one of them arose within one month and several of them rose in half a year or one year.

In the next column, I looked at the presence of carcinoma in situ, and without counting up the pluses and minuses, carcinoma in situ was present in nine out of 11 of the cases in the orlistat end of the trial and in two out of three of the placebo end. What that tells you is that there was a precursor lesion in the breast which had been present for many years before those patients were actually put on orlistat.

In the next column I'm looking at grade of the tumor. Now, the lowest grade of tumor, invasive cancer, that you can get in the breast is Grade 1 and the highest grade is Grade 3. Oh, sorry. My mistake. It took me so long to do this last night I'm still tired.

I put in this column type. Now, type I regard as quite important. I've abbreviated ductile to D. I've abbreviated lobular to L, and I have used the abbreviation T for tribular. Now, tribular is simply a very, very well differentiated from a malignant ductile cancer.

But the take home message from this column is that there is complete heterogeneity of tumor type. It is not a uniform tumor type that you see in here, and that's what one would have expected, I think, had orlistat been causally related to its development.

And in the next one, I'm looking here at grade, and in grade as I was about to say earlier, grade is -- the lowest type is Type 1 and the highest is Type 3, and what you might expect of an agent that was causally related is that the grade, in fact, would be similar if not identical, and it isn't, and I will present the numbers later without you calculating them yourself.

In the next column I've looked at lymph node metastasis, and as you can see NA simply indicates that there was no information on lymph node metastasis or the axilla had not been sampled, and that happens in some clinics.

But where they were sampled, lymph nodes were very frequently involved, and that's indicated by a plus sign and the actual numbers of lymph nodes involved are in my report.

What that tells you is that those tumors were around for quite a long time because we generally believe in the clinic that these tumors, when they have lymph node metastasis, have been around for several years at least.

Then the penultimate column is the tumor size. Now, tumor size varies in this column from seven millimeters. There's actually one there which I see is greater than six, but I'm taking seven as the smallest, ranging up to 25 millimeters, and it's from that data I calculated when that tumor was likely to have arisen.

And in the final slide of this rather complex series of data is the overall conclusion, and the overall conclusion is that the bulk of these tumors preexisted orlistat introduction, and those are

all indicated in yellow. You will find that there are four exceptions, and those four exceptions, two of them are in the orlistat end of the study and two are in the placebo arm of the trial.

Now, if you look at this data another way, what one can derive is as follows. Here are the original figures in the N column of incidence, and the ones which preexisted according to my calculations, that number, in fact, on the hard copy which you have in front of you is nine -- sorry. It's the other way around. On the hard copy it's nine. Up there it's eight. I don't know how that typo was introduced because it was done last night.

Anyway, it doesn't really make a whole lot of difference because we can calculate that nine of these tumors -- that includes one case of carcinoma in situ, which I indicated is not a true cancer anyway because it's not invaded -- can be accounted for as preexisting before orlistat was introduced to the patient, and similarly, in the placebo the same data as given.

However, one has to say that in the blocked arm here of this table that there are two cases, two in the orlistat and two in the placebo arm of the trial, which could possibly, but I regard as

unlikely to be related to orlistat therapy causally, but one has to concede that possibility, but there were two in each arm of the trial.

Now, the summary of the evidence, because there was quite a lot of it on that slide, I've summarized here. The presence of CIS tells me that in the bulk of these cases, nine out of 11 in the orlistat end of the trial, that the high risk lesion had been present for years.

The second point is that I would have expected had orlistat been causally related tumor type homogeneity, but what we found, in fact, was heterogeneity, similarly with grade.

Lymph node metastasis tells us on the penultimate bullet that the tumor had been around for a long time, and so also did the calculations which were done on tumor doubling time.

And from all of this data, it is my view that there is no evidence at all that orlistat is causally related to breast cancer initiation or promotion, and there is a typo there. It should say "or."

The next slide simply demonstrates that this is not my sole opinion. There were independent assessors involved here. Three of them were

pathologists, and I have to tell you that I didn't call any of them once, nor did I communicate in any other way with them or they with me, and we all came to exactly the same conclusion. They, however, didn't all look at the slides that I did. In one case there were in excess of 75 slides, by the way.

And it is also compatible with the information which Dr. Feig has produced, which is in your volume and which is on that rather complex table, the hard copy of which you have in front of you, where he looked at mammograms that preexisted the -- predated the study randomization and when the tumor was figured out.

So there was complete concordance between all of these individuals on the causality issue, namely, that orlistat was not causally related to tumor development in the breast.

Now I want to turn to issue two. The hypothesis has been put forward that did orlistat enhance the growth of -- I'm sorry. My mistake.

The next hard copy which you have in front of you, yes, this has jumped.

Right. Did orlistat, in fact, enhance the growth of preexisting tumor in the breast? Right. The preclinical evidence that Dr. Anderson has

presented indicates that that is unlikely. I'm now going to evaluate the human pathology data to see whether, in fact, this may be the case.

But before doing so I will tell you what my overall conclusion is going to be at the end of it all, namely, that there is no evidence to indicate that orlistat, in fact, does enhance tumor growth.

Right. Now, what criteria were used here? If you're going to put forward the hypothesis that growth enhancement does occur, you have to suppose that one of two things happened. The first thing is that there could have been an increase in cell proliferation, or the second is that there could have been a decrease in cell death, and both of those would have produced larger tumors more rapidly.

And the way these were assessed is indicated here. If this hypothesis was correct, I would have assumed that the invasive cancers would all been of high grade because they would have had to be proliferating at a very high rate.

The second thing that I would have supposed would have happened or predicted that would have happened from this hypothesis is that the CIS lesions would have been high grade because if you were to hypothesize that orlistat came along and stimulated

a preexisting CIS lesion, it would have to proliferate more rapidly, and that would be evident microscopically.

The third criterion here is that you would have to support also that if orlistat were having an enhancing effect, you might also see changes in the adjacent non-tumorous breast, and that was looked for.

The second and very last point on this slide, namely, decreased cell death, I'm not going to report quantitative data on that. I simply looked for apoptosis, and I can tell you right now I didn't find any difference at all in the two groups.

Going on to the next slide, and I don't know whether you can dim the lights easily. If you can't, forget it.

Grading of tumors and invasive cancers in particular is actually quite easy.

Can I operate it from here?

Grading of invasive cancers is actually quite easy. What I've shown on the left is a Grade 1 tumor, and on the right is a Grade 3 tumor. In a Grade 1 tumor, you see these nice, little tribules (phonetic), and that's normally what you would expect to find in a well differentiated tumor, and the cells that compose those tribules are very regular looking.

A Grade 3 tumor, on the other hand, you can see that these cells are very large and very different, and the word used in histopathology terminology is nuclear pleomorphism.

However, you can actually do some quantitation on tumor grade, and this is actually how it's done, and this is the recognized way in which it's done all over the world, including in the Armed Forces Institute of Pathology, which is I regard as one of your most prestigious pathology institutes.

Going through this, there are three elements in quantifying grade. You look at, first of all, differentiation. You look at nuclear morphology, and you look at proliferation rates, namely, mitoses, and depending on the amount of differentiation you get, as indicates up there, you allocate the tumor a certain number of points.

And having gone through these three things here in a formal way, you can come out with a total point score, and the total point score is indicated here in yellow on the bottom right, and it indicates that quantitatively you can quite easily define a Grade 1, 2, and 3 tumor, and to remind you Grade 1 is the best tumor prognostically, and Grade 3 is the worst.

On the next slide I also said that what you would expect in an enhancing situation is that the DCIS might change. Well, it doesn't. On the left you have got low grade DCIS at low PER and high PER, and on the right you have got high grade DCIS.

Now, even for the non-pathologists in the audience, I think that's really quite a profound difference. In low grade DCIS -- is actually still forming tribules here. It isn't on the opposite side where it's high grade. At a higher magnification, those cells are fairly regular, and those cells in the higher grade are very, very irregular.

I would point out that every micrograph, and I'm only going to show you one more, that has been taken for presentation here today has been taken at exactly the same magnification, and so what you're seeing is not only the reality, but the true and absolute reality if you believe that there are absolutes in this world.

Now, finally, or penultimately, the other prediction from the hypothesis, the enhancement hypothesis, would be that what you might expect to find is that in the post menopausal breast you would have stimulation of the surrounding non-tumorous epithelium.

Now, what I'm showing you here on the left is a typical post menopausal breast, and in fact, this photograph was taken last Friday just before I left, and that is from a 60 year old woman. That on the right, believe it or not, is from a 70 year old woman who had also breast cancer. Both of these patients had breast cancer, but that patient there -- and this photograph is taken at exactly the same magnification, times ten as you can see in the bottom right-hand corner, you don't actually have to be a pathologist to see that there is profound stimulation here and none here.

Now, the obvious question you're going to ask me in the discussion is why is there proliferation in this woman's breast, and I will address that very briefly.

Right. This is a summary of the evidence, and it is present in the hard copy. this is a summary of the evidence in the hard copy before you, and what I try to do here is I've looked at proliferation, and the tumor grade is heterogeneous throughout those tumors in the orlistat arm of the trial and also in the placebo arm of the trial.

There was one Grade 1 tumor. There were seven Grade 2 tumors, and there were two Grade 3

tumors. That's over the study as a whole.

If you look at the CIS to see if there was a lot of proliferation there, there wasn't, but CIS was present in nine of 11 patients in the orlistat arm of the trial and in two of three in the placebo arm of the trial.

And if you look at the very last page of my report in Volume 2 under McGee, you will actually find the numbers of patients with high, low, and intermediate nuclear grade type CIS.

And thirdly under the proliferation issue in terms of predictions, there was no evidence that I could find that orlistat stimulated the proliferation of the non-tumorous epithelium in the surrounding breast. As I said earlier, I looked specifically for apoptosis to see whether there was any decrease, and I didn't find any decrease at all.

And on my last slide, it is my very firm view that there is no cell biologic or pathologic evidence to indicate that orlistat enhances tumor growth from the information and all the slides that I've examined.

Thank you very much, indeed, for your attention.

CHAIRMAN BONE: Thank you.

DR. McGEE: Mr. Chairman, do you want me to remain for questions or shall I sit down?

CHAIRMAN BONE: Yes, please do. Yes, I'm sure there'll be a number of them, starting with Dr. Hirsch.

DR. HIRSCH: Yes. Help clarify two points. First of all, what in the general population is the ratio of ductile to lobular malignancies overall, not in this population?

DR. McGEE: The answer is 13 percent.

DR. HIRSCH: Is what?

DR. McGEE: Thirteen of lobulars, the rest ductiles.

DR. HIRSCH: In this population you have about a 50-50.

DR. McGEE: Yeah.

DR. HIRSCH: The population I'm now referring to is the treated group, and the other very interesting thing, I can't do a chi squared in my head. I'm very sorry.

DR. McGEE: Nor can I, so I hope you don't ask me

DR. HIRSCH: It turns out that if you make a one year cut, which seems to be a sort of reasonable place of where antecedent tumors might have expressed

themselves, there's an enormously enhanced lobular ones. It's 80 percent lobular and 17 percent ductile.

On the other hand, after one years, it's reversed. It's 83 percent ductile and 20 percent lobular.

The likelihood of that being a chance occurrence, it seems to me, is rather remote. So there is a sort of progression here of different histologic types emerging. Can you help me with that?

DR. McGEE: Well, yes, I can help you with that because up until about eight years ago I didn't believe the data on lobular cancer and its instance, and there's a very famous pathologist, who's now retired, whose name was Asaparde (phonetic), and I invited him to the department to give a seminar on the classification of breast cancer, and he stated that the instance of lobular cancer was 13 to 15 percent in the general population.

Now, he'd been looking at breast cancers like for 40 years, and I said to him, I said, "Look. I've rarely diagnosed lobular cancer," and that, therefore, you could take a chance as well, and I think that's probably the explanation here. I don't think you can make a derivation like that or a conclusion like that from the information in front of

you, and had I not had this experience with Asaparde, who worked in the Hammersmith in London, I might have, in fact, agreed with you, but the numbers are too small anyway, I think, to do the sort of analysis that one would want to do statistically.

DR. HIRSCH: So you're telling me that the diagnosis of histologic type is under question. Is that what --

DR. McGEE: No, no, no, no, no, no. I think the question that you're asking me was does the fact that there are a lot of lobular cancers in the first year indicate something special is going on. Un-huh?

DR. HIRSCH: Un-huh.

DR. McGEE: Right. No, I think the answer is no because I think the numbers in there are far too small, and my reference to or analogy to Asaparde was that up until about, as I said, seven or eight years ago I hadn't really diagnosed lobular cancer. I'm diagnosing it more now, and that's not because I'm a better pathologist.

DR. HIRSCH: But right now what's the ratio of the two in the population at large, would you say? Your own experience at the moment?

DR. McGEE: Well, I think actually to

quote from one's own experience is anecdotal, but I would say anecdotally it's about 20 percent as one. It's about a fifth, and the literature actually more or less agrees with that.

DR. HIRSCH: Thank you.

DR. McGEE: Yeah.

CHAIRMAN BONE: Other questions? Dr. Ellis and then we'll go around.

DR. ELLIS: With respect to the hormone hypothesis that was looked at earlier with respect to analyzing the estrogen levels in patients and deciding there was no difference, the first part of my question relates to estrogen receptor analysis and was there any analysis done.

DR. McGEE: Yes, there was. Now, I'm passing this question across to Dr. Huber not because I'm afraid to answer it, but when I did the analysis blinded originally, I looked at all of those slides which were provided to me, and there were only, in fact, two cases in there which actually did ER and PR. ER is the abbreviation for estrogen receptor, PR for progesterone receptor analysis by histochemistry.

However, Hoffman-LaRoche has gone into this a whole lot more carefully since then, and Dr. Huber has some data which I would like him to show

you.

DR. HUBER: Martin Huber.

This data is not based on our own one analysis. This is based on the reports obtained from the sites that we were able to track down. So may I have the slide, please?

And simply to show you, this is once again the same format. Patients here, orlistat 120, orlistat 60, placebo; day of diagnosis for reference, and what you can see here on the ER/PR status, we have -- it's kind of mixed, positive and negative.

With regards to not known, it's important to note, for example, this patient here NM1430240, this was the patient that was the carcinoma in situ, and so there was not a sufficient sample to do the analysis. The remaining samples where it's not known are primarily, if you notice the little B here, those are the ones that come from Europe, and we've had less success, shall we say, in tracking down that information.

To the best of our knowledge, this is all of the ER/PR data that we can find.

DR. McGEE: And can I come in now?

CHAIRMAN BONE: Sure.

DR. McGEE: I would just like to add a

rejoinder or to amplify that answer. From your accent you're obviously English, and we haven't met before.

(Laughter.)

DR. McGEE: My accent is Scottish, by the way, which is north of the border from England.

The question of ER and PR analysis. Although in the United States, and because of my involvement in breast cancer I visit quite frequently, it's almost done as a routine. Now, that is not the case in Europe. It is not through lack of effort that these pieces of data have not been available. It is that there are no guidelines even in the U.K. that you have to do PR and ER analysis.

Until about a year ago when it was decided that cancer centers were going to be created all over the U.K., and one of the criteria in there was that you had to do ER and PR, although I have been campaigning for it for years; so it will now become available in every patient, but I'm trying to explain the reason for the unavailability of the data in some cases.

CHAIRMAN BONE: All right.

DR. ELLIS: Thank you. I just have one other question. It relates to stromal changes because, of course, there's a very interesting

observation in the rats with a decrease in the frequency of fibroadenomas. Did you see any stromal changes that you could in any way relate to orlistat treatment?

DR. McGEE: The answer to that question is, very briefly, no, not because I looked at the question trivially. I did not because as I said, when I went into this study, I went in blinded, and I had a protocol. I had a protocol sheet, and I had listed a whole lot of questions to which I was going to record the answer.

One was what did the stroma look like, so that I was recording every fact. There was no difference whatsoever in the stroma between the two, placebo and also the orlistat arm of the trial.

DR. ELLIS: Thank you.

DR. McGEE: I don't understand why the fibroadenomas have gone down, by the way.

CHAIRMAN BONE: Yes, Dr. Sherwin, did you have a question?

DR. SHERWIN: Yeah, two questions of information. The effect of estrogen on breast pathology in terms of cancer, is there any difference between lobular and ductile? In other words --

DR. McGEE: I think the question you're

asking me is does --

DR. SHERWIN: The propensity, the slight increase in risk associated with estrogen therapy. Does that increase --

DR. McGEE: No.

DR. SHERWIN: -- the risk of which kind of cancer?

DR. McGEE: No, it is not.

DR. SHERWIN: Okay. My second --

DR. McGEE: Is the brief answer.

DR. SHERWIN: Okay. My second question is related to apoptosis. Your assay was tunnel assay or --

DR. McGEE: Well, no. I'm glad you asked that question, and I truly am because the way I assessed apoptosis was not the tunnel assay. That's what I would like to have done. What I did do was to look, without going into morphologic criteria, but I will if you want, was to look for the usual morphologic criteria of apoptosis on an H&E section.

What that tends to do, of course, is it makes it a little more difficult to quantify, but not impossible, and what it will do versus the tunnel assay is to give you a lower number than you might have expected, but the ratio will still be the same.

Yeah.

DR. SHERWIN: Right, but --

DR. McGEE: And the reason -- the reason for not doing the tunnel assay was that I could only be provided with the original slides from the primary diagnostic pathologist and not extra sections, which is something that I would have liked to have done and will do, in fact.

DR. SHERWIN: Would you agree that your power or ability to detect differences in apoptosis might be more limited compared to the stimulation assessment?

DR. McGEE: Yeah. Well, no. It turns out that I actually know the man who discovered apoptosis, and his name is Care (phonetic). He's an Australian, and a Scotsman called Andrew Wiley (phonetic). The reason I mention that is when apoptosis was first described way back in the '70s when I was a boy professionally, I actually -- why are you laughing? -- I wondered, you know, why they were interested in this because I thought, you know, this can't be an important issue because I didn't see it very often.

But I then went back into the literature to see, in fact, why they had become interested in it, and they discovered it in basal cell cancers of the

skin. If you look at basal cell cancers of the skin -- after I saw this, I went back -- they are so easy to identify, but they had been called all sorts of things, as you probably know, like eosinophilic bodies, et cetera, et cetera, but they were proven, of course, to be apoptotic cells.

So they are actually very easy to see, but just to reiterate what I was saying earlier, the only difference between the standard methodology that they used when they discovered apoptosis in the '70s and the tunnel assay is that the tunnel assay might give you an absolutely higher number, and it might change the ratio a little bit, but I think it wouldn't change it greatly.

CHAIRMAN BONE: Dr. New.

DR. NEW: Could you tell me whether any of the patients were examined for the known breast cancer mutations?

DR. McGEE: Now, someone else in the Roche team may be able to help on that, but I think that the point that you bring up is something that I regard as very important, and it's very important for the Committee to realize and also for the rest of the audience to realize, and this relates to a question that your Chairman asked earlier, namely, growth

suppressants or tumor suppressant compounds that might, in fact, be absorbed, is that what you should remember is that out there people who have breast cancer, only five percent of them at most, five percent can be accounted for by mutations in either BRCA 1, 2, the hypothetical 3 or 4 gene.

So the likelihood is out of 15 cancers that you've got in here, you're likely to see five percent. Now, that is not a roundabout way of me avoiding the answer. I'm just pointing that out for information.

But I'll pass over to Dr. Huber now because he may, in fact, have gone into this in more detail.

DR. NEW: Could you also tell me anything about the ethnic groups?

DR. HUBER: Okay. No specific information was available with regards to molecular markers. With regards to risk, the only thing we were able to capture, that was the risk factor information. That is actually available in the table on page 92, Table 64, I believe, in the first volume of your briefing document. And if you want to go into detail, we can talk about that.

With regards to ethnic groups, I mean,

it's a European-U.S. population, and I think there were -- yeah, it was all white.

CHAIRMAN BONE: Other questions from the Committee? Yes, Dr. Siegel.

DR. SIEGEL: Two questions. Was there any abnormality at all in the surrounding tissue around these tumors that in some way distinguished the nonmalignant breast tissue from other nonmalignant breast tissue that you would see in breast cancer patients?

DR. McGEE: None whatsoever.

DR. SIEGEL: Okay.

DR. McGEE: And I should point out that if you go back on my bibliography and hit the Medline button, in 1975 or up until about 1975, my predominant interest, in fact, was collagen connective tissue and not molecular genetics, and in fact, that was one of the problems I looked at in breast, namely, why there was a difference in stroma in breast cancers. So that was something that I looked at very carefully for in the surrounding breast and didn't find it.

DR. SIEGEL: And the second question, which is the major thing that I've been thinking about all morning is that if this drug were in some unexplained way a promoter of breast cancer growth,

would not the data that you suggested, doubling time of 100 days, 150 days, 200 days -- you know, is that valid if we were in a situation where, you know, this drug were actually accelerating the growth?

I noticed that when you looked at tumor grades, I didn't remember any Grade 1s in the tumors that were seen in the study group. I mean overall it's not only more lobular than I would expect to see, but also, you know, overall higher tendency for high grade.

You know, could it be that the doubling times that you were using may be invalid if, indeed, this effect were occurring?

DR. McGEE: Yes, but I've done the doubling times with various variations, and you will find, in fact, in the volume under Wright -- I think it's Volume 2, but it's tagged in any case -- we give the confidence intervals because the calculations were done for a doubling time of 121 days, for the median doubling time in a normal -- when I say "normal," a non-exposed population to any known agent -- of 157 days, and the other at 204 days.

And even if you go down to 121 days and assume that all of the ones, if you believed the enhancement hypothesis, and do the calculation of 121,

it still wouldn't explain it.

DR. SIEGEL: I mean, lobular cancers, in general, are less easily detected mammographically.

DR. McGEE: Yes.

DR. SIEGEL: And, you know, is it the case here that perhaps with this, you know, there was a threshold effect, that the tumors were more easily picked up because they were lobular and because, you know, they were stimulated?

Again, I'm just asking that kind of question. The profile here is a little different than what I see and, I'm sure, what you see in the breast population.

DR. McGEE: Yeah, I mean, I have to say that -- well, I'll take your question in two parts. First of all, the mammographic statement which you made. The mammographic statement is that lobular cancers are very much more difficult to detect radiologically than ductile cancers, and Dr. Feig, who's an expert, and I'm not, in mammography, can address this issue if he would care to add anything to that.

But I am not convinced that the apparent preponderance of lobular cancers in this first year are statistically meaningful. I think that that is

just pure chance, and I can offer no other explanation than that.

And maybe the epidemiologists here, the people who are very much better at numbers than I am, can do the statistical analysis on that this afternoon.

Dr. Feig, would you like to make some comment on mammography?

DR. FEIG: Well, with respect to lobular carcinoma in situ, LCIS, we really don't see it on mammography. When we see micro calcifications and they're biopsied and the pathology comes back lobular carcinoma in situ or lobular neoplasias, as we prefer the term, the calcifications are really not in the area of the cancer. They're adjacent to it, and LCIS is a fortuitous finding really.

With respect to invasive lobular carcinoma, it is more difficult to detect mammographically than invasive ductile carcinoma, and that's based on the pathologic pattern of growth. It doesn't distort the tissue as much. It doesn't create masses as much. It looks like vague densities that many in some cases resemble normal breast tissue.

CHAIRMAN BONE: Thank you.

I think next is Dr. Ellis and we'll go

around to anybody else.

DR. McGEE: Can I just say one other thing about the lobular story and the question which has been put to me by two gentlemen about the preponderance?

I would actually like those people who are good at mathematics, better than I am, to do some sort of arithmetic.

DR. HIRSCH: It is highly significant I almost certainly believe.

DR. McGEE: Well, I haven't done that. All that I would say is that looking at all of those lobular cancers from memory, and if you consult the very last page of my report, I think they were all either Grade 2 -- I don't think there was any Grade 3. In other words, there was no evidence that the proliferative rate in those cancers was stimulated.

You'll find it in the -- I think it's in the fifth column of the very last page of where McGee is tagged in Volume 2.

CHAIRMAN BONE: Right, and then we'll have Dr. Ellis' question.

DR. ELLIS: I guess this is more in the form of a hypothesis. Obviously women who lose weight, and who are treated with orlistat are losing

more weight than the placebo group, have changes in their breasts. First of all, the breasts do decrease in size, and that could lead to a preexisting palpable mass becoming more prominent because obviously adipose tissue will decrease relative to the breast mass.

And the other question -- now, that's sort of a self-evident thing. The second thing relates to mammography and whether weight loss could alter interpretation of mammograms or make breast masses become more prominent or easy to diagnose, perhaps particularly for this lobular subtype which is very difficult to diagnose on a mammograph and, indeed, by clinical palpation.

DR. McGEE: Yeah. I would rightly say that because I'm not an epidemiologist, I couldn't explain the overall increase or apparent imbalance between the orlistat and the placebo end of the trial, and instinctively I thought about the hypothesis that you're putting forward.

The patients who are losing weight become more body conscious, become more health conscious, and you know, they admire themselves more, and without going into any more detail than that, I think, you know, that they would be more inclined to do self-palpation, et cetera.

So that was my notion, but I was told by the epidemiologists that that was foolish.

However, I think on the second issue that you mentioned, namely, would it be more easy to pick these up in women who lost weight, Dr. Feig is much more able to answer that than I.

DR. FEIG: Well, the answer to that question is, yes, it certainly is possible because with the weight loss, if you have a decrease in breast volume, the breast could become more compressible, and when the breast becomes more compressible, the breast tissue can be placed closer to the film, and so you have a sharper image.

You also may have more contrast, the image, because as the breast thickness decreases, it will affect the scattering of radiation in the breast itself that can be related to the contrast. So although there are no studies, you know, to back this up, intuitively it does certainly make a lot of sense that if breasts become more compressible due to weight loss, that the image quality will improve and you may be able to see mammographic lesions better.

DR. ELLIS: Thank you.

CHAIRMAN BONE: I think the question that Dr. Hirsch was just raising was whether there was an

unusual degree of weight loss in these women in whom the breast malignancies were detected.

DR. HUBER: We looked at this, and if I can have the slide, please. This is, once again, the same format, the same patients, day of diagnosis. Now, this is their baseline BMI, and this is the weight change, and we notice we had several patients who do have extensive weight loss of approximately ten kilograms. We also had other patients who were, you know, minus two kilograms.

An important point to note, however, if you look at these two patients here in NM14302, Patients 2 and 3 on this list, you notice minus .1 and 2.9. This study was actually a regain study. So these patients had actually lost substantially more weight prior. So this is based on strictly from the time they started orlistat. In fact, the patients over the preceding six months had also lost about eight to ten kilograms.

CHAIRMAN BONE: But presumably they have a control group.

PARTICIPANT: That's correct.

CHAIRMAN BONE: Yeah. It looks to me like there were only two patients there that had above average weight loss compared to the general orlistat

experience, and the rest actually had quite a bit smaller than your --

DR. HUBER: But like I said, this is kilograms, not percent.

CHAIRMAN BONE: Yes.

DR. HIRSCH: But the question though is the difference between the placebo and the other group, and there's no reason to believe that with a four percent difference in weight loss you're going to suddenly, you know, make things appear that weren't before. There's no evidence for that, nor is there any evidence that people are more health conscious or less, whatever, placebo versus treatment group. So I don't think any of that's right.

CHAIRMAN BONE: All right. Further questions related to these presentations?

I had one, and then we'll come back to Dr. Ellis.

This is for Dr. McGee, for Professor McGee.

You had discussed the heterogeneity of the lesions with respect to their grade, and I wondered if you were looking at the post menopausal women receiving estrogen replacement therapy, you'd expect to see after a period of time a modest, although not

a very large, increase in the risk of breast cancer.

Would these excess breast malignancies have any special pattern with regard to their grade?

DR. McGEE: The answer to that is no. That was a very hard answer for me to get because all of the work on HRT virtually is epidemiological, this 1.3 relative risk increase, and about two weeks ago I must have spent at least half a day on the telephone calling up all of my colleagues who are best experts to tell me was there anything in the literature that I had missed in terms of what the cancers themselves and HRT showed or what the surrounding breast epithelium showed because that was one obvious thing that one should look at if you're looking at a known, quote, stimulate like HRT, what you would expect to find in the adjacent non-tumorous breast.

I eventually got to the bottom of it, and this publication is coming from the Patterson Institute in Manchester in the U.K. and will be published in the British Journal of Cancer by as far as I know next month.

But in summary, they did look at the epithelium in the breast and surrounding breast, and they didn't find any difference at all morphologically, but what they also did was they

quantified in a nice way the proliferation rates within the surrounding breast in these patients with tumors, and in the Key 67 index -- Key 67, for those of you who are not pathologists, Key 67 is a very good marker. In fact, it's the best marker currently available for cycling cells.

And they didn't do a trivial study. They did a very large number of patients, and they counted 900 cells from every one of these patients, and the bottom line on that is that they only showed that there were 0.3 percent of cells cycling in these patients on HRT, and the premenopausal value is 0.5 to five percent, in spite of the fact that those women were on an HRT that had taken a level theoretically up to what it should have been premenopausally, and that's rather interesting in that we don't know why HRT has this 1.3 relative risk increase because it's certainly not reflected in the tumor type or in the adjacent epithelium, as you might have predicted.

CHAIRMAN BONE: Thank you very much.

Dr. Ellis.

DR. ELLIS: The question relates, I suppose, in response to Dr. Hirsch's point that there's no evidence for the hypothesis that weight loss might be associated with improvement in breast

cancer detection. I agree with his point, but, on the other hand, that might be data that's not so difficult to obtain.

My earlier point concerning breast morformitry (phonetic) or some information about changes in breast size in the trials might speak to that.

Also many of these women have received mammograms, and many of their mammograms were, of course, normal, but nonetheless, those mammograms could be examined blindly as to whether they were before or after a period of weight loss to see whether an experienced mammographer was able to tell which of the mammograms was taken after the period of weight loss. Those kind of things could be done.

CHAIRMAN BONE: All right. A final question or point from Dr. -- well, let's say Dr. Sherwin and then back to Dr. Hirsch, sticking again to Dr. McGee's presentation.

DR. SHERWIN: I may not be right because it's not my field, but I would expect an eight to ten pound weight loss in a 220 pound woman or a 200 pound woman as having a very modest effect on breast size and the amount of fat mass within the breast. Is there evidence that you would lose more breast mass

than in the rest of the body?

DR. McGEE: I'm not the best person to answer that question. I could do anecdotally by the response of my wife gave me, but I shall not tell you.

CHAIRMAN BONE: Right, okay. Thank you.

And Dr. Hirsch.

DR. HIRSCH: Yes. You remind me of something now with all of this, and it's the following thing. If there's 20 grams of loss of fat per day in the stool, the prediction would be that this is not a random group of fatty acids ingested, but is a selected group because we know that saturates, for example, tend to be excreted more than others. There are cis-trans differences in fatty acids, et cetera.

Now, the way to analyze whether this does or does not have an effect is to look at adipose tissue fatty acid analysis along this lengthy year or two study of those who were on placebo versus those who were on drug. This would give an answer to that.

Was that ever done?

DR. McGEE: I would like to call Dr. --

DR. HAUPTMAN: You mean looking directly at adipose tissue?

DR. HIRSCH: That is correct.

DR. HAUPTMAN: We didn't measure adipose

tissue. We did measure some essential fatty acids in the serum, and we saw essentially no changes for omega 6 and omega 3s. So over the long time of the study, we expect that we didn't see any of the changes in the serum. We didn't think we would see any things in the tissue.

DR. HIRSCH: The adipose tissue would be the only integrated marker that would cast light on this, I believe.

CHAIRMAN BONE: All right. Thank you.

If there's no further questions for Professor McGee, are we through then with the sponsor presentation?

DR. McGEE: Thank you very much.

CHAIRMAN BONE: Thank you.

DR. HAUPTMAN: I will just close up very briefly.

When we originally had put it together, I said that we had seen a lot of data this morning, and I guess now afternoon, and I'll see what I can do to get everyone to lunch as soon as possible.

But we did see a lot of data today, and I would like to put it into perspective. There are three key points to be reconsidered: safety and tolerability, the conclusions related to breast

cancer, and the efficacy for both changes in body weight and improvements in risk factors.

When we look at the overall safety, we found the drug was generally well tolerated. We identified some effects on fat soluble vitamins, and as we said before, we believe patients taking orlistat should have fat soluble vitamins as part of their overall treatment.

But nothing in the nature of orlistat suggests any inherent potential to cause or enhance the development of breast cancer.

Orlistat works by partially inhibiting gastrointestinal lipases, thereby producing a modest increase in fecal fat, as we heard, 20 grams per day. There are no other pharmacologic effects of orlistat or its metabolites seen in a wide array of testing. There are no significant findings seen a broad, extensive array of toxicologic or carcinogenic testing. In man there is very minimal systemic absorption of the drug.

Regarding the unexpected imbalance as seen in the reporting of cases during this study, several lines of converging evidence have shown that the majority of the 11 patients who had breast cancer during the studies actually had it before ever being

randomized into the program, and that there is no causal association between orlistat administration and these events.

Why the 11 patients were not equally distributed among the different groups during the randomization process is not known, but what is known is that some of these patients were already in the process of having breast masses and abnormal mammograms worked up at the time they entered the study.

In addition, a thorough survey extending the observation on patients to an average of three and a half years shows that few cases other than those identified early in the study were seen. Two additional patients on placebo were identified, as were two on orlistat.

Because of the 90 percent response rate and the high rate of mammography in these patients during the post treatment period, it is likely that most new findings would have been identified.

After a very thorough and detailed evaluation of this problem, as we've discussed today, there is no plausible evidence of a biologic association. The most plausible explanation as to why more patients with breast cancer were randomized into

the 120 milligram dose group is that this is a chance finding. You can only conclude the findings are due to chance after other reasonable avenues of investigation have been explored and found lacking, which is what we believe we've done in the ten months that have occurred since the last Advisory Committee meeting.

In considering a possible direct effect of the drug as a cause, orlistat is, if anything, only minimally absorbed, and there is no evidence of accumulation of drug over two full years of dosing.

Also, looking at a known indirect of the drug, such as decreases in fat soluble vitamins as a possible cause, almost all patients with breast cancer had fat soluble vitamin levels that were consistently normal and, in fact, by the end of the study many of the patients' values were similar to the way they were before starting drug.

Regarding growth enhancement, all of the data that we have, both clinically and non-clinically, provide no evidence for growth stimulation with orlistat. If cancers were stimulated for any significant length of time by a drug, we would expect the increased finding of tumors for some time even after the drug was stopped. In fact, this did not

occur.

To implicate orlistat either directly or indirectly as cause of these findings based almost completely on the observation of events without considering any potential explanation for these events can produce a misleading conclusion.

It is clear nine events in the orlistat 120 milligram group is greater than one event in the placebo group. No one argues that fact. We believe that these findings have a reasonable explanation which we have discussed openly and fully today.

Later today you'll be asked the following question: taking into consideration the overall benefits and risks of orlistat, including the increased incidence of breast cancer in the controlled clinical studies, do you recommend that the drug be approved for the treatment of obesity?

And we agree that during the clinical trials there were a greater number of breast cancers detected in orlistat patients, but the real question is: is there an increased risk for breast cancer with orlistat treatment? And the weight of all of the evidence clearly shows there is not an increased risk.

Most of the patients had breast cancer at the time they entered the study. Orlistat does not

cause or stimulate breast cancer. A thorough review of the data provides no plausible evidence of a biologic association with orlistat treatment.

And please consider the following when you discuss this matter: the opinions of well respected breast cancer experts that you have heard here today or you saw the reports in your briefing document, including experts referred to us by the FDA, are consistent in that they agree there is no causal association with orlistat treatment.

Briefly turning our attention to efficacy, patients treated with orlistat had a greater mean weight loss over time. Twice as many patients on orlistat reached the level of weight loss in which medical benefits begin. Patients with orlistat had diminished weight regain, and the drug was effective long term.

And the reason why there's no more data in the literature regarding long term benefits of weight loss is because up until now, with the single exception of surgical intervention, there has been no effective long term treatment available.

We showed you the results of four large, two year studies that were, again, consistent in their effect.

Regarding improvement of obesity related risk factors, such as cardiovascular disease profiles, the Lipid Research Clinic data show for every one percent decrease in cholesterol, there's a two percent decrease in cardiovascular risk.

To review our data, orlistat lowered LDL cholesterol by an additional eight to ten percent compared to the placebo group, and the LDL/HDL ratio decreased by 50 percent more than those patients in placebo.

The benefits of weight loss on lowering blood pressure are well known. Studies have shown that for every kilogram of body weight loss, there's a one to one and a half millimeter of mercury decrease in diastolic blood pressure.

In our studies, patients with preexisting diastolic hypertension at baseline who were treated with orlistat and lost weight had a decrease of eight millimeters of mercury. Some of that decrease obviously is due to the extra weight loss the patients had, but please remember two to three times more patients can achieve a medically acceptable amount of weight loss with orlistat.

We looked at overall effects on carbohydrate metabolism. Patients treated with

orlistat had significant improvements in glucose, insulin, and C peptide responses. Our data show that far more people who are obese and have impaired glucose tolerance normalized on orlistat compared to placebo, and far fewer patients who had impaired glucose tolerance went on to become diabetic than the placebo group.

Also, patients who were already known to be diabetic receiving oral hypoglycemic medication had decreased need for medication and improvements in overall diabetic control.

So what does all of this mean to a person with medically significant obesity? With the addition of orlistat as part of your therapy, a person with obesity will lose more weight and keep that weight off long term and will have lower obesity related risks.

As for the physician, orlistat provides an option for pharmacologic treatment that is not an anorectic, that does not work in the central nervous system, and has minimal systemic bioavailability, and importantly, has been evaluated in a large, at risk population for up to two years.

Orlistat is probably the most thoroughly and extensively studied and evaluated pharmacologic agent for the treatment of obesity. Nevertheless, as

part of an ongoing process that is similar to all new drugs, we have initiated and planned a large number of Phase 3(b) and Phase 4 studies to continue to evaluate all aspects of orlistat's efficacy and safety in over 20,000 patients in well controlled and mostly double blind studies.

Based on all of the data that we've looked at this morning, considering the overall tolerability, the safety and efficacy, and safety, as well as efficacy, we can conclude the following: that when administered as part of an overall weight control program in patients with medically significant obesity, orlistat is generally well tolerated, has a good safety profile, and is effective in producing and maintaining clinically meaningful weight loss resulting in improvements in obesity related risk factors.

CHAIRMAN BONE: Thank you.

I take it that does then conclude the sponsor's presentation. Very well. I have 1:18, and I'm afraid we're going to have to resume at two o'clock with a very short lunch break.

(Whereupon, at 1:20 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:03 p.m.)

CHAIRMAN BONE: We are going to next have the presentations by the people from the Food and Drug Administration, and the first speaker will be -- let me just make sure we have everybody here that we need. Who are we missing from the -- I'm sorry. We do have one or two Committee members that are on their way, I'm quite sure. They'll probably be here in any minute, and I think considering this is a relatively short presentation, we'd like to make sure they're all here.

I'm sorry. I've got everybody sitting down in order a little head of time here because I didn't realize we had one or two people left to come, but it's good for us all to be in order. It will help our lunches to settle which we've ingested at an excessive rate.

Thank you.

(Whereupon, the foregoing matter went off the record at 2:05 p.m. and went back on the record at 2:06 p.m.)

CHAIRMAN BONE: I think everyone's here now for the Committee, except where is Dr. Siegel? Oh, right there. Very good.

We will begin now with the presentation by Dr. Stadel from the Food and Drug Administration.

DR. STADEL: If I could have the first slide of the background, yeah.

This issue came to our attention really in the fall of 1996 when Dr. Colman noticed that there was some excess in breast cancer when he was doing the review and brought it to me, and we had some discussions with the company.

It was then gone over in an initial way at the May Advisory Committee in '97, as was discussed, and there was some concern expressed at the end by the Committee about desirability of further data, and so that has been done.

You've heard much of it. I will be discussing our perspective of it. If I might have the next slide.

This is just a brief reminder of the nature of the data set. There are a total of seven trials, three one-year trials, two two-year trials, and two two-year crossover studies with reassignment of drug at the end of one year.

There's then a space you see there at the end of the trials. There's then a substantial period of time between the end of trials in early '96 and the

telephone survey of women over 45, which was carried out between July and October of '97. So there is a substantial follow-up time period that we'll be dealing with.

These trials were in both Europe and the United States, and they were all state-of-the-art, placebo controlled, double blind, and so forth.

Randomization was carried out in two strata, depending on how much weight the patients lost during the lead-in period, and in most of the studies this was a four to five-week lead-in period. In the one weight regain study it was a six-month lead-in period.

If we can go to the next slide, well, these are the data we've been concerned about. This covers the events that occurred on treatment during the trials. These were the initial data that we looked at, and which raised the concern. I'd like to speak briefly about these patients.

They were all Caucasian women who were over 45, 45 or older, at the time of randomization to drug or to placebo. This in and of itself is not at all surprising. Breast cancer is much more common in the peri and post menopausal years than in younger women, so that the fact that the issue arises there is

not at all surprising.

Their age range at diagnosis was 46 to 61 years, which is commensurate with the population studied. Four of the 11 came from the randomization strata that had lost less than two kilograms, less than or equal to two kilograms, or in one study less than or equal to ten percent of initial weight, and seven came from the other strata.

I raise this simply in noting that they did not come from some particular part of the overall structure of the trials. That will be true in other ways, that is, that they permeate four of the seven trials, generally larger trials, so that the excess is scattered through the trial program and comes from both components of the randomization stratum.

If we can go to the next slide, this is what occurred while patients were on treatment. This is before the follow-up study and gives the time to diagnosis for the three groups. As you see, the placebo.

The 30 to 60 we combined because the groups were small and because there was only one case at these lower doses, which were also less effective for weight loss.

And then you have the comparison here.

The probability is a comparison of the 120 milligram three times a day dose to placebo, having a P value of .04.

A question was raised, I think a good one. A difficulty in interpreting these data that's been discussed a lot, so I'll interface with it now, is the issue of various ideas about plausibility of mechanisms. So one question I was asked is: well, what happens if you exclude the first 100 days? That would exclude the first two cases here. You would then have a P value of .15, and you would have an odds ratio of five and a half, with a lower bound of .84 going up to 124.7.

So the direction would be the same, but, of course, if you exclude some of the data, the significance would go down. The pattern itself obviously visually does not change.

Now, having seen these data, there was a question, very important question. Well, this is what happened on treatment. So one question is: what happened among dropouts or withdrawals before the end of the time on trial? That's one question because it has to do with intent to treat analysis of the trial population.

A second question is: what happens in a

reasonable period of time after the trials are over? Is there catch-up? This would clearly greatly change the interpretation.

So after the trial time was over, as we've discussed earlier, in July through October of '97, an effort was made to contact the women who had been over 45 at the time of randomization. Eighty-nine percent of the women were contacted with very, very close rates of contact across the different treatment arms.

So if we can now go to the next slide, we will see -- oops. I always miss this one. I'm sorry. Let's go ahead to the next slide and we'll come back to this one.

This is what you found in the follow-up period, that is, there was only the addition of two cases on drug and of one case that we have counted on placebo.

Now, a third case on placebo has been mentioned. However, it was reported spontaneously after the end of the period of the time when there was complete ascertainment of breast cancer across the follow-up study. So I would submit that it is just not appropriate for inclusion in analysis. You don't know what you would have learned from the other people had they been followed through. You might have found

other cases. So I have limited the analysis not to include that.

As you can see, whatever is going on here is dramatically something that goes on while the drug is being taken. It does not continue when people are off treatment.

Now, I do want to go back, if I might. This is our own dose response analysis that is based upon actual person-time. The preceding slides were based upon cases occurring in terms of the number of people randomized initially.

What this shows, I have actually used six groupings for the doses because we are dealing with a mixture of trials. There were two crossover trials. So what I've tried to do is to say, well, if one took -- how does one construct a hierarchy of doses? Clearly the top dose is that you were taking 120 all the time you were on drug, and there were 944 person-years in women over 45 at randomization who were taking 120, and they had an incidence in that period of 8.5 per 1,000.

Then there was one case diagnosed in the group that had been on 120 and was crossed over to 60. So I put it as the second strongest dose, that is, on 60 at the time of diagnosis, but having had a prior

year's exposure to 120.

Well, that gives a rate of 20. Of course, it's based on one case, so the number itself is not very stable.

You then had 60 milligrams, and you had 314 person-years on 60 milligrams with a rate of 3.2; 81 person-years on 30 milligrams. There was only one study with the 30 milligram arm, and nothing there.

Then you had people who were on placebo, but had had a prior year's exposure to 120 in a crossover trial. They had no cases in 104 person-years, and then there's the straight placebo group.

When doses are ordered in this way and actual person-time on treatment is used, the P value of test of trend is .05.

Now, if we could go -- now, this again will just go over -- now, this brings us back to an overall statement based again now back on intent to treat status. This uses the drug that you were initially randomized to as the denominator, which as we've seen is actually very close approximation to person-time experience.

Since this has uniform follow-up for all arms, I think that using the simple intent to treat analysis is a conservative and appropriate way to

analyze the data. There's 88 to 89 percent follow-up across all of the arms through the entire period of time, including a long follow-up period after the studies were over in the beginning of '96 all the way through mid-'97, and we see a .04 P value for 120 versus placebo.

Again, this would be reduced if one chooses to discount the initial cases, say, in the first 100 days, which I mentioned earlier what the effect of that discounting would be. It would be a very similar effect here.

So these are basic data. We will now get into possible explanations if we go to the next slide. Possible explanations I think include three: detection bias, chance, and causality.

Detection bias would occur under one of two circumstances. Either examinations were more frequent for the group on 120 compared to the other groups or at an equivalent rate of examination the probability of detection at any given examination was increased, and of course, both possibilities could commingle. I will address these to the best of my ability.

First, descriptively, of the nine women who were on drug while they were diagnosed, five were

routine mammography, that is, country specific mammographic protocols, and so on. One was a routine physical exam, and three were for biopsies of symptomatic breast masses. I don't know why the masses became symptomatic. That I'm not sure of from what I have distilled from the case reports.

In the one woman who was on 60 milligrams, her diagnosis began with an examination that was prior to an elective breast surgery. She was going to undergo breast reduction surgery and was picked up then, and in the one case diagnosed on placebo, it began with a routine mammography.

So there's a mixture of events. So I'm going to look now in some bit at the possibility that weight loss due to taking orlistat might have led to the earlier or to the more frequent diagnosis.

And if we could go to the next slide, this, to begin, gives the same actual slide that was shown by the sponsor. It's ordered to the left by the time between randomization and the proximate weighing, that is, usually the one just before, which is appropriate, just before diagnosis to give you the spread by time and to show the weight change from that baseline randomization time until that immediately before diagnosis and show the distribution for you for

the patients who were diagnosed on treatment for the 11, and you can see the numbers there.

This, I think, shows up a little better on the next one which gives you a bar graph. This is for the group as a percent of weight change, percent change from baseline, and what you see is that there were two patients who had quite substantial weight loss. I suppose if more of them had been like that it would be easier for me to imagine that weight loss was responsible, but, in fact, the weight changes are quite modest.

You notice the weight change for the others, you know, are not very large. One of them is actually an increase. One is none at all, and then there are some small changes.

Another way to look at this is to look at each study, if we may go to the next slide, each study in which a breast cancer case was diagnosed and to look at the weight of that patient at the time of diagnosis, plot it against lines which show the mean weight for women over 45 at randomization. This is not the whole data set. This is the group we're concerned about.

And what we see here is in the first study we look at, the red is the placebo, and that one

actually had lost less weight than the average of the placebo group. The 60 milligram one over here on the left in yellow was actually on the mean line for the 120 group, but notice it's before the lines have diverged hardly at all. There just isn't much difference.

And then the one other 120 in this slide is actually -- her weight at diagnosis was right on the mean for the placebo group. So that this is the first of the four studies.

Now we go to the next one. Here we only had one, and it's in the middle. You see? It's a little difficult. It's over on the right between 92 and 104 weeks, and it's in the middle between the placebo mean and the orlistat mean.

And we go to the third slide. This is the one -- no, next one. Here we have one that's on the left, you know, is on the mean for the 120 group, one that's in the middle between the two, and then one that is down on the mean for the 120 group.

And we'll go on to the next one, and this is -- something is wrong here. Back up, please, one slide. We should have two cases that are below, and I think something's happened.

PARTICIPANT: It's the first one you

showed. Back up one more.

DR. STADEL: I'm sorry. I thought it was on this one. Let's go back to the first one, and we'll just quickly look through this. One more. Sure enough. I apologize for that.

Yeah, the two that -- you know, if you look way down here, the two that had lost a lot, they're way outside the group, and there one would have had more feel for plausibility. I got my attention drawn to the color scheme rather than the full number of Xes.

So if we can go quickly back then just through them and go right on to the end, to the last one of those. Yeah, back. Okay, and that's the weight regain study. That's why the weights are going up. Patients were on a six-month run-in and then were treated to see if you could retard weight regain, and there you see that the two cases are split between.

So from this I find it difficult to see that there is a pattern of weight loss that is plausibly connectable to the likelihood of diagnosis.

I would also point out that were detection bias the explanation, one might expect the rate in the placebo group to have caught up. There was a rather long follow-up period after the trials were over.

But let's go on with other detection bias possibilities. Now, in the telephone surveys that were conducted after the trials were over, the first survey was getting at that issue of whether there were excess cases, and in both the first wave and the second wave there were questions of mammography. I've brought those questions together here.

This one asks the woman -- now, this is interviewing her in July through October of '97 and asking her about the frequency of mammography in the five years before interview. So if you think back, that would cover pretty much the clinical trial interval.

So it would tell you what differences were, and if you look at the left-hand column, you see that those who reported that they had yearly mammograms, 37 percent of placebo; interestingly 64 percent of the small, 30 milligram group that didn't have any cases diagnosed in it; 37 percent of the 60 milligram group that had one case diagnosed in it; and 46 percent in the 120.

Now, these differences are a little more apparent than real because I'll actually read a statement submitted by the company. "The apparent difference between the 30 milligram group and the

other treatments is due to the fact that the 30 milligram dose was studied only in one of the studies, NM14302, the weight loss maintenance study. Controlling for study, there are no statistically significant differences between treatments."

And also if you look and you add together the percents for yearly versus every two years, you see that, in fact, 37 percent plus 26 gets you 63, and 48 plus 21 gets you 67. So they get very close.

So that it does not look like there were large differences in the frequency of mammography while the women were on the trial to account for the magnitude of the difference in the frequency of breast cancer detected.

If we could go to the next slide, now this other question -- I will add a caveat to the previous. You're going to have to go back. The response rate to that question was between 73 and 78 percent across the treatments. So that's a fair number of women interviewed who didn't respond. So my conclusion is that within the restriction, there is some nonresponse to the question. There is nothing notable known about the nonresponse. That is, it does not appear to have been differential, to my knowledge.

If we go to this one, the response rate

here was pretty much like it was in the survey as a whole, that is, 87, 88, 89 percent. Actually it was by arm 89 percent, 87, 82, and 88, response rates to the questions among the women surveyed.

And you see here that since the end of the trials there were a very similar pattern to the other, that is, you had a slightly higher rate of mammography in the 30 milligram group, but it was a very small number of women, and otherwise, why, the rates are really quite close to one another.

Those are the points I want to make about the likelihood of detection bias. One is that I don't see anything in the weight loss of the women who received diagnoses of breast cancer which would support the idea that their weight loss led to an earlier detection, and I don't see anything in the frequency of mammography by treatment arm that would support any kind of selective increase in examinations by women in the 120 arm compared to the other arm.

Now, I would add a caveat. We do not have information on things like breast self-examination. I have no reason to postulate that it would be different. I'm just saying that I do not have data on it. I do not myself think it's very plausible that it would be different in a blinded trial. So anything's

possible.

The next slide goes to something that's been discussed earlier so I'm only going to need to mention briefly. I didn't put the whole list up. It was shown earlier by representatives from the company. I chose some variables simply to illustrate that randomization, in fact, did achieve a very, very good balance at baseline.

Now, I would think in that regard that it probably also achieved a good balance in women who might have had small breast tumors at the time of randomization. Women over 45, breast cancer is a common occurrence. I will show some numbers later on, how frequently it's diagnosed in the United States. So at any given time, a group of women who have not undergone mammographic screening for a study can be expected to have a distribution throughout that population of small breast lesions. The question is: why do they become diagnosed in one group and not in another?

So I'm certainly not disagreeing with the argument that's been made that something was present at the time of randomization. I think that's very plausible, and I think the question is why it wound up in one group compared to another.

The history of hormone replacement therapy here you see was raised as being a little higher than some people might expect. That leads into a comment that was related to a question Dr. Marcus had raised, and I will mention that it looks like the trial population was probably a little more medical care users than the national populations from which it was recruited.

In particular, one case of cancer was diagnosed on trial in the placebo group. One, point, six were expected from the national population. So the trial population was a little lower risk as a population, and I think the proper comparison there is to compare the placebo rate to the national rate, not to do relative risks that use national rates as the base. I think we're all in agreement that the right comparison is arm to arm.

Now, when you take the whole follow-up period in, we had two cases in the expected. On the national basis for the combined U.S. SEER and European IARC data was four, 4.26. So, again, I think it's not surprising that a group of women recruited to be in weight loss studies would probably come from parts of the population that were more likely to be screened in the past than average. So it's not surprising that

the rate of breast cancer in the placebo group was slightly lower than in the nations from which the groups were recruited. I think actually that that makes sense.

Okay. The next slide brings together our own computations, which is really a representation of one of the slides I show earlier. It is just a numeric closure, if you will, and it shows that over this entire period beginning with the beginning of the trials in 1992, the actual end of the trials in early '96, and then a full follow-up through the middle of '97 that you had 11 cases of breast cancer diagnosed in the high dose orlistat group, 120 milligram t.i.d., and one case in the 30/60, and two in the placebo group, the one that was diagnosed on treatment and the one that was in a dropout off treatment.

Now, the test of trend here is using the intent to treat group. It's not person-time like the one I did myself with the six categories, but the answer is really not greatly different, and that is there's a small probability of it occurring by chance. The P value here is a little low because it's an intent to treat analysis rather than one that uses person-time, but I do not myself think that those small variations in how you compute the P values are

of enormous importance here.

The odds ratio for the primary comparison you can see there of 120 versus placebo has an odds of 4.3. The way our statisticians computed the confidence interval has a lower interval of 1.1. That involves what's called a mid-peak correction which can be discussed with our statisticians if you wish, and a .05 P value.

So that brings together the main things that I have to say about the trial experience. I'm just looking through to see if there -- I think that's pretty much the main points that I have to make about the trial experience itself.

The last comments I wish to make have to do with -- well, let's go to the next slide, the conclusion slide, the anti-obesity drug use slide, yeah.

Now we will shift gears a little bit, and this is to try to get in perspective. Here we have these results from the clinical trial. They're unexpected. They haven't been replicated. The P values are not testing of a previously formulated hypothesis. They are this is what was observed. So it hasn't undergone the most rigorous test of all, which is replication. Does it repeat if you do a

similar scope of trial database, by far the best test of such a finding?

But I wanted to talk about what happens in the United States right now briefly. In 1997, there were about 18 million scripts written for weight loss drugs of one sort or another. Now, that included the peak and valley of the story in this country with phenfloramine and phentermine. The peak was in the summer and it began to fall off.

So it also means that some of these were two prescriptions per patient if they were on phen-phen. I don't know how many prescriptions per patient. So I'm not even going to try to say how many patients.

I cite it to point out that it was a large -- there was a large weight loss market. It peaked in the summer. You know, it's now dropped off. About a quarter of it was women over 45.

So there's a large population of potential people who might be exposed to a new weight loss product. That's really the only intent of this slide.

And the next one. The next one is to convey that in 1997, given the age distribution of women in this country at last year, the rate of breast cancer diagnosis under 20 to 44 -- you don't get

breast cancer diagnosed much under the age of 20 -- was as you see one in 1,472, whereas over the age of 40, 45 and over, one in 319 women in this country received a diagnosis of breast cancer.

So I think the purpose of putting it up is for you to imagine regardless of how you interpret what we do and do not know with the trial data, the potential intercept between the prescribing of a weight loss program and the receipt of a breast cancer diagnosis, I see this as a very difficult scenario from an FDA standpoint, and formerly being with the Epidemiology Branch at one time dealing with adverse event reports and so forth.

I wish to point out what the intercept might be when there is a question left nagging about a problem.

And then we'll go right to the end. So my conclusions, over the entire period one in 68 of the women originally randomized to 120 milligram t.i.d., who were over 45, 45 or over, at the age of randomization received a diagnosis of breast cancer compared to one in 316 on the intermediate doses and one in 234 on the placebo.

The last slide. We went through detection bias. I do not see any evidence for detection bias,

and I see some substantial amount of evidence which I consider to weigh against detection bias.

Chance is a possibility of course. The finding has not been independently replicated. Our calculations of the statistics give a bit narrower window to chance than the calculations previously presented, but I think we could all agree that it's out in the realm somewhere out here that this says, well, maybe that's chance and maybe it isn't.

If it isn't, what is it? Well, we don't know. There has been some discussion earlier about the pathology, about possible biological mechanisms, and I think that these are appropriate discussions. I do not have any immediate answer to them.

I do not know what accounts for the finding of the trial, but I know that I can't discount it. I've looked through the possible explanations. I do think that the data are consistent with the possibility that something is stimulating a rapid increase in the size of a lump which is making it diagnosable while the people are on drug and that whatever that is goes away promptly.

That is speculation. I'm simply describing to you what I see in the data because I cannot explain it on the basis of detection bias, and

other than that, maybe it's chance.

thank you.

CHAIRMAN BONE: Thank you, Dr. Stadel.

I think there may be some questions from members of the Committee for Dr. Stadel. Dr. Marcus.

DR. MARCUS: Thank you.

That was the usual lucid presentation that I've heard from you over the years, and I really enjoy them and benefit from them. I appreciate that.

I've tried to ask this earlier, and the answer I've gotten hasn't satisfied me. Perhaps you can do it.

DR. STADEL: I'll try again.

DR. MARCUS: My understanding is that there is a linear significant relationship between incidence of breast cancer in years post menopause in this country. That is, as you start on average age 50 and you go to page 51, 52, and up, the incidence of breast cancer rises progressively.

DR. STADEL: It does rise, not linear, but it does rise progressively.

DR. MARCUS: Okay. The women in this trial -- and I certainly accept and understand fully that for determining relative risk, the important comparison is within the arms of the trial among each

other and to placebo. That is not what I'm getting at.

The attributable risk, that is to say, the number of cancers that you might then be able to calculate would exist in society if given a given relative risk, is critically dependent on what the background incidence of cancer is, which may be higher in this overall study group simply because they were on average five years post menopause, not actually just verging on menopause, which is because of their apparently early menopause.

DR. STADEL: Yes, I'll try. I think I can answer. Two comments.

One is actually the average age at natural menopause in the United States when it was last measured was about 50, but you have to add to that the effect of artificial menopause, which has increased in the recent decades, so that the average age at menopause has to factor those two.

I have not in this trial population calculated the average age at natural menopause among those women not having had a surgical menopause. I don't have any reason to believe it's unusual.

DR. MARCUS: I see.

DR. STADEL: My guess is that the numbers

you're seeing represent the mixture of surgical procedures with naturally occurring menopause.

I see heads nodding here. So I don't think there's any disagreement that that's likely.

DR. MARCUS: That's a very good point, and I thank you for that.

DR. STADEL: The next point is that I did try to address earlier and has to do with what is the relationship of the occurrence or the diagnosis of breast cancer in this clinical trial population to the rate of diagnosis of breast cancer in the United States as a whole. Well, actually since the trial was done in the U.S. and Europe, what they did -- and that part was very helpful. Table 4 and 5 in Volume 3 of your submission I think may be of help here. I believe those are the right ones. Yeah, I pulled them out, yes.

If you look at especially Table 5 because it subsumes the whole story, Table 5 tells you, if you look at the line for placebo that's on page 101, and if you look at the line in Table 5 where it says placebo, it gives you the expected number of breast cancer cases in the placebo arm of the trial for women starting at 45 to 49 because they were 45 at randomization, and going across the age groups and

then accumulating them.

Then you're saying if you had taken a random sample of women from the United States, which is covered by the SEER system -- at least a portion of the U.S. is covered by the SEER system actually -- and the parts of Europe covered by the International Agency for Research on Cancer, that if you had taken an equal number of women randomly and followed them for the duration of the clinical trial plus the follow-up through mid-'97, you would expect that four of them would have received a diagnosis of breast cancer instead of the two that received a diagnosis.

I view that as saying that there's not a great difference between the trial population and the national populations. I mean if it had been ten, then there would have been a much higher risk or if it had been none you wouldn't know, but, in fact, to get two when the expected is four is not terribly different.

And I think what that tells you if you look actually at the structure of these trials, multi-center, they were very well designed to be representative trials to try to look at the effect of weight loss drugs in a large, appropriate population, I think, and consequently their breast cancer experience in the placebo group is not greatly

different than that of women. It's a little lower in the trial than it is in the population.

So I think that gives you a frame of reference. It says the trial population was a little lower risk, probably a little more medicalized. They may go to the doctor more often. So some cases identified; so the population as a whole, a little lower risk, but not greatly different.

DR. MARCUS: Thank you.

Just to think of the logistics of trying to take a next step, if one wants to really nail down what the result of putting people on this medication, women over the age of 45, by an independently designed, prospective trial, you'd have to ask yourself what percentage increase would you want to detect to be able to make the power. If you wanted to see a 500 percent increase, then you have fewer people than if you wanted to see a ten percent increase.

So let me just assume since the public is certainly interested to know about the small increase that is attributed to estrogen, which we seem by consensus here to have adopted as a 30 percent increase, there are four million women about who are above 45 who received an anti-obesity drug last year, and that would have led to 13,000 cases of breast

cancer, given the table.

How feasible is it to design a trial? How many people would be involved? How many years would be necessary to demonstrate a 30 percent increase in breast cancer?

DR. STADEL: I will address what I think are some of the constraints that would be involved. I do not have the actual power calculations available, but I think it would be helpful.

First, given these findings, if one set out to say, well, we're going to do a trial and we want to find out if there's an increase in breast cancer, given what you already know, you would have to include a screening mammogram at baseline and exclude from study those people with any evidence of small tumors because of the possibility raised by these data that the drug is somehow accelerating such.

Now, that means that their expected rate of diagnosis would be, over the next year or two, would be much lower than it is here because you'd have screened out the people with smoldering, if you will, small foci of abnormality that might or might not grow onward, you know, to become diagnosed.

So we have raised this issue. So the first constraint is that you would have to base the

power calculation on the rate of diagnosis subsequent to a baseline screen from an area where you were planning to do the trial, and you'd have to have an area that had a large enough mammographic screening program that would make it possible to say, well, okay, here is a group of screened women. We know what to expect.

Then one would have to calculate the sample size on that basis, and that's not something I can do without knowing actually where it would be done, you know.

DR. MARCUS: Can you give me a ball park -- this is my last -- can you give me a ball park estimate of whether you think that this really is the kind of question that can come out only in a post marketing, intensive surveillance as opposed to actually being determined by a prospective clinical trial?

DR. STADEL: I would hesitate to give an answer. I really apologize. I would hesitate to give a sort of yes or no answer to that. I'd have to see what resources were available, see the power calculations, all actually laid out, you know, what was logistically feasible to do before.

I'd also mention that one of the things

that's been raised in general discussions about this, is to say, look, if you design a trial and we're doing this trial to find out whether this drug increases breast cancer, that you can't do that.

You would have to then do it in a population where you could reasonably say that with the baseline screen -- now, suppose you took a group of people who have a medical disorder for whom it is known that weight loss actually improves health outcome, as opposed to the large body of weight loss, which the best available data we have says that weight loss in people who do not have established illnesses, hypertension or Type 2 diabetes, doesn't seem to have much impact on mortality, but does have an impact -- intentional weight loss -- in what data we have available when the person has hypertension or diabetes mellitus or -- those are really the two large groups.

So that if one said, well, look, if I could find a large enough -- a place where I could do, say, a large study, there you could justify it because you'd say, look, we're going to -- we know that weight loss benefits you. You'll reduce the load of medications, reduce risk rising, and if you have a baseline screen, and if we have a rule that says if we reach a set level of increase that we would stop;

under those circumstances, I don't foresee myself that there would be any ethical dilemma.

But all of those constraints come into play before the power calculations and feasibility that you're asking for could be worked out, and that's why I must say I don't feel I could give an answer in terms of numbers.

CHAIRMAN BONE: Obviously one of the major, perhaps the dominant point would be what magnitude of increased risk you were trying to detect. At 30 percent versus 100 percent or something like that would make a huge difference in what you --

DR. STADEL: And, you know, usually as a practical matter when one gets down to doing it, what you do is plot a series of power curves that show the tradeoff between size and detectability, and then someone would have to pass judgment on what was acceptable.

And, again, what was acceptable is a level, is a measure of uncertainty, you know, what the limits were, would depend on what the benefit-risk tradeoff overall was for the group of people. If they were people who had a substantial illness profile, then you would tolerate more, and so forth, and it would have to be calculated in that way.

CHAIRMAN BONE: Thank you for that discussion, Dr. Stadel.

Dr. Critchlow.

DR. CRITCHLOW: One thing that I'm trying to reconcile is given the mammographic screening coverage, I mean, about 85 percent of the women in the trial had at least one mammogram in the previous five years, and given the conclusions reached by the pathologists that most of these tumors were present for quite some time, why do you think these weren't picked up?

DR. STADEL: Well, now, wait a minute. The give years is five years prior to July to October 1997. It's not at baseline, at randomization or prior to that.

So I don't know what their history was actually, say, in the year --

DR. CRITCHLOW: So that was just prior to the '97, and the first trial was in '92?

DR. STADEL: The first trial started in the beginning in '92. We could put that slide back up here.

DR. CRITCHLOW: One and two were '92, and the rest of them were '93, four.

DR. STADEL: '92 and '93, yeah.

DR. CRITCHLOW: Somewhere in there.

DR. STADEL: And then you're asked in the past five years.

DR. CRITCHLOW: So most of those then -- that question really was directed at or it essentially covered post enrollment in the studies probably.

PARTICIPANT: We do have specific information on these cases if you want that.

DR. STADEL: Yeah, okay.

CHAIRMAN BONE: On the cases. The comment was that the sponsor has information on the individual cases about what screening they'd had beforehand, but not for the trial as a whole, I presume.

DR. STADEL: Yeah, it's the trial population. You know, it's --

DR. CRITCHLOW: There's no information on that.

DR. STADEL: It's interesting actually. As you say it, you know, you have this '92, '93 and you're saying back to five years for interval did you have them annually. I guess all I can say is --

DR. CRITCHLOW: I mean it was every year for some and another third were every two years, and other ones were --

DR. STADEL: Yeah, is that, one, only a

portion of them said that they had had them every year.

DR. CRITCHLOW: Right. It was like 25 percent.

DR. STADEL: Two, you're dealing with interview information as opposed to actually dealing with baseline mammograms, and that's about the best I know.

I think you raise an interesting point, but the quality of the data is not as intense as if you had baseline screens.

CHAIRMAN BONE: All right. Let's see. Dr. Molitch.

DR. MOLITCH: Just trying to get at this question of detection and ascertainment bias and the possibility that there might be a difference with weight loss, et cetera, and many of the mammograms that are done are not done because something is felt, but because they are just sort of routine annual mammograms or screening mammograms.

And I was wondering if -- and so that might dilute things out perhaps -- I was wondering if there were any data that the sponsor has or if you, in looking at the data, were able to find out how many actual breast biopsies were done that were either

benign or malignant and were those different between the two groups.

DR. STADEL: We do have actually in that interview survey -- was a question, and maybe we should try to bring that. I can read it to you. That is covered though, yeah.

Now, this, again, is in '97 okay. '97 women are asked have you had a breast biopsy, and --

MR. MOLITCH: Wasn't that only in response to the mammogram question?

DR. STADEL: No.

DR. MOLITCH: Okay.

DR. STADEL: This is in the frequency of breast cancer risk factors part.

DR. MOLITCH: Right.

DR. STADEL: Yeah, right. Now, in the 120 milligram group, 18 percent said they had a history of breast biopsy. That doesn't tell you when it occurred.

DR. MOLITCH: Right.

DR. STADEL: Sixteen --

DR. MOLITCH: Not subsequent to starting this study?

DR. STADEL: No. You see, it's a question that simply was -- it's an effort to get at whether

there was any difference in risk factors, you know. It's not what you want, I'm afraid.

I don't think there is trial specific surveillance that tells you by arm what the -- how many women --

CHAIRMAN BONE: Those data should be available at least as raw data because that would be considered an adverse experience and would be recorded.

DR. STADEL: Well, unless it was performed off protocol. I mean, if it was performed off protocol, it may or may not have gotten noted. I don't see that there was any --

CHAIRMAN BONE: But during the study --

DR. STADEL: Okay, okay.

CHAIRMAN BONE: -- on protocol, they probably should have that at least for the on protocol time.

DR. STADEL: Yeah.

CHAIRMAN BONE: All right?

DR. STADEL: Because as I understand for the reporting of mammography is pretty much catch as catch can. If women had a country specific mammogram, those were recorded for cases. They're in the case histories where they had them, but they wouldn't have

been recorded in the protocol, would they, routinely as part of the medical update history for all women in the study?

I mean, maybe they are. That just wasn't my understanding, is that one would not have -- there was not a question that said each time the woman came in, "Have you had a mammogram in the past since we last saw you?"

CHAIRMAN BONE: You would be more likely to have the biopsies.

DR. STADEL: Okay, and if they have that, yeah.

CHAIRMAN BONE: All right. Let's go on then to other questions. Dr. Cara had a question for Dr. Stadel concerning his presentation.

DR. CARA: A lot of what people have said in terms of trying to explain this occurrence of an increased incidence of breast cancer is that it's happening by chance. I'm trying to figure out whether or not we can use the odds ratio to tell us what it is or what is the chance of this actually happening by chance.

DR. STADEL: Well, actually if you want to know the chance per se, use the P value. How many times in 100 would this occur as a fluke? Our P

values are generally -- in the dose response analysis, it was .02. In the intend to treat analysis, .04. If you discard the first two cases it goes up to .15, and so forth.

DR. CARA: Okay, but what that's telling you is that there's a greater than 95 -- well, whatever that would be. I mean .02 would be 98 percent chance that it's --

DR. STADEL: Not due to chance. Yeah, in that analysis, yes. The .02, and I think the dose response on actual person-time on drug myself is the most information specific analysis I did. There, in that particular one, it's .05. The dose response by intent to treat status over the entire period was .02.

I think so you're dealing somewhere in that range. You're dealing with a relatively small likelihood of those findings simply occurring as a random phenomenon.

CHAIRMAN BONE: Let's see. We had a question or comment from Dr. Simon.

DR. SIMON: It's not really a question. It's just a comment on the last question.

I guess my own view -- I don't know that this is the time to -- I think I'll explain it later -- is that the P value is not the proper way to

interpret this body of data because there are several important factors that it doesn't take into account. I'll go into that a little bit later.

CHAIRMAN BONE: Maybe that's best covered in the discussion.

DR. SIMON: Yeah.

CHAIRMAN BONE: Let's finish up with questions regarding Dr. Stadel's presentation and then we can go on to Dr. Colman.

Others?

(No response.)

CHAIRMAN BONE: Fine. Thank you very much, Dr. Stadel.

DR. STADEL: Thank you.

CHAIRMAN BONE: Next will be the final -- I'm sorry? -- yes, the concluding remarks, I guess, by Dr. Colman are scheduled.

DR. COLMAN: Yes. I think in the interest of time because Dr. Stadel summed things up so well I'll just make a brief comment.

There's certainly been a lot of discussion about the causal relationship between the drug and the breast cancer and certainly a hesitancy to accept that causal relationship because of the lack of biological plausibility, and it just reminds me of a similar

situation I just want to mention.

You know, if 25 years ago I were to tell you that a bacteria caused ulcers, you would laugh me out of the room. So I think we need to be a little careful before we discount a relationship simply because we don't at this time have a mechanism to explain it.

CHAIRMAN BONE: Thank you, Dr. Colman.

I think now would be an appropriate time for general discussion by the members of the Committee and our guests.

We have, as you know, three invited guests, one from the Oncology Committee and two other invited guest experts, and I think perhaps we'd start with their comments and then come to the other members of the Committee, and we may as well start with Dr. Simon who appears eager to begin the discussion.

DR. SIMON: Well, I mean, I think actually this application illustrates why P values are not really the proper way and the whole answer in terms of interpreting this body of data, and it's really because there are two factors that they don't consider -- it doesn't consider.

One is in any sort of a quantitative analysis of this data, we have to take into account

that a priori this finding was unexpected. It was not like we were starting out on a clinical trial to see whether the treatment was effective for weight loss. That's not the endpoint we're looking at here.

And in terms of assessing whether we, at the end, whether we believed that the study drug causes an increase in breast cancer, in assessing that we need to take into account that a priori the finding was not expected. That's not to say biological mechanism, but a priori however you look at it there could be some mechanism. We don't know what it is. It was not an expected finding.

The second thing I think we need to take into account is that the statistical power for finding this result was lousy, and when you consider the size of the effect that was found for breast cancer, if you were going to go about planning a trial to detect that size of effect, you would have had to plan a much larger trial, and that needs to play a role in the quantitative assessment of what we believe about the result.

And the third factor that I think needs to be taken into account is that in the P value itself there is some uncertainty as to what we would all feel comfortable with a P value. There was one case that

was not cancer, and there's two cases that were detected very early after randomization, and so the P value, however we calculate it, may be somewhere between .05 and .15, but exactly what it is, you know, is subjective.

So you can actually calculate using your prior probability that you believe -- that you expected an effect, say, of a relative risk of at least three for breast cancer at the outset, and if I said that a priori I think there's one chance in 100 that the relative risk for breast cancer will be three or more, and if I take into consideration the fact that the power for detecting an effect of this size is probably about 30 or 40 percent, and if I use the fact that if the P value maybe is .10, something like that, or .15, in that range, then my probability after seeing the data, after seeing this P value, my posterior probability of a relative risk -- that this drug causes a relative risk of breast cancer of at least three is only about four or five percent.

So finding a P value of .05 to .15 on a very unexpected endpoint with very poor power is very weak evidence that there's any real risk of breast cancer here.

CHAIRMAN BONE: Well, let's just have the

others. Dr. Siegel?

DR. SIEGEL: Can I just ask some questions?

First of all, these trials with the study drug were for one year or for two years. When you're talking about making this available to the public, is this a drug that will be used indefinitely? It will be used for a year or two years?

DR. HAUPTMAN: We studied it for two years -- John Hauptman -- we studied it for two years to give the practicing physician the ability to treat patients for up to two years based on the safety that was established, but the individual length of time that an individual would be on the drug is a decision between the doctor and the physician (sic), and we just provided the criteria that you need to make a decision of how long you wanted to treat the patient.

CHAIRMAN BONE: Dr. Siegel, maybe I can help you to understand this. Until fairly recently anorectic agents were approved only for short term use, and under the new guidance, which includes not only anorectic agents but, for example, this agent, the practical period of use contemplated is essentially indefinite. This is for long term use, would be the registration.

DR. SIEGEL: Because where I'm coming from with this is that, you know, I don't know. I don't think that we've proven that there's a problem, but I don't think we've disproven that there's a problem, and that's kind of where I'm coming from.

When we make analogies to the use of estrogen replacement or we're talking about people who are on for years, and in fact the people that develop the -- if they do develop a higher risk of breast cancer, it's after ten years of use, and here we're talking about after a year or two. So that's part of, you know, the thing I'm trying to resolve, and maybe if you want to comment on that.

DR. HAUPTMAN: Yeah, the comment is that in terms of the length of time of use, that it only should be used if it's being effective so that there's benefit for the patient over the long term. If the patient regains their weight or doesn't lose weight, there's clearly no benefit, and that patient should stop the drug at that time.

So any extended use would be for patients that have extended benefit.

DR. SIEGEL: If I could ask Dr. Feig, one question is that you, in your section of the volumes, had mentioned that there were a number of these, I

think, either four or five that were, you know, retrospectively viewed to be present before the drug was ever started, and what wasn't clear in reading your section was whether you had correlated -- whether the abnormalities that you were seeing on the mammogram actually were the cancers that were resected because what you can do as a mammographer is identify abnormalities. The diagnoses are made pathologically, and you know, just in my own experience in treating a fair number of breast cancer patients, it turns out that sometimes they don't always correlate. There may be a mammographic abnormality that wasn't that.

That's something that's important in trying to interpret the data.

DR. FEIG: Yes. Well, going through my report here, the mammographic findings were fairly firm in that one case, there was speculation that was seen retrospectively, and the cancer was a spiculated carcinoma. So in that case and in others, for instance, it wasn't just an island of asymmetric tissue in which a cancer subsequently developed. The cancer could be seen actually in retrospect.

The second case were clustered micro calcifications and then a soft tissue density developed around them. So I think that's likely, but

it's not as strong as the first case.

The third case a spiculated nodule that then developed into a spiculated carcinoma, and that was also -- the fourth case was the same thing. So this was not a case where, say, you had a benign mass, such as a fibroid, and a carcinoma developed in it that wasn't really related to it, but this indicates that it really was the carcinoma that was there initially rather than two different processes being present at the same location.

CHAIRMAN BONE: Did you have further questions or comments at the moment?

DR. SIEGEL: I'll stop.

CHAIRMAN BONE: Thank you.

DR. SIEGEL: I'll let somebody else.

CHAIRMAN BONE: Dr. Ellis.

DR. ELLIS: As an essentially practical individual, I was just wondering if, say, theoretically you said that this drug should be approved, but you would put in some kind of warning which said patient would require a thorough physical examination and mammography before the drug would be safe to administer, how many of the cases would actually have not received the drug in that case, looking at the clinical details?

I mean it strikes me that at least two, possibly three patients already had mammographic abnormalities that were in the process of being investigated for these, and several of the cancers were quite advanced when the diagnosis was subsequently made, and I wonder whether a more thorough evaluation before the drug was started might have picked those up.

I wonder if that's a fair way of looking at it, but I wondered if we could have a comment on that.

DR. HAUPTMAN: I can give you probably some other information that you would find useful. We have a study that's ongoing in Sweden called the Zendo study. It's approximately 1,800 women are on that study. In that study we asked the patients to have a pretreatment mammography.

Of the 1,800 patients with a pretreatment mammography, 24 were found to have abnormal mammography. Two were Stage 5, two were Stage 4, which is possible or probable likelihood of cancer, and 20 were Stage 3, which generally about a third of those go on to be a tumor.

So altogether we estimate that about eight patients with breast cancer were prevented from

entering that study, and so you can make any analogy you want from there.

CHAIRMAN BONE: Let me just ask a follow-up question, if I may about that particular study. That's rather interesting. How long term is the exposure in that study?

DR. HAUPTMAN: That will be at least a two year study.

CHAIRMAN BONE: And when was it initiated?

DR. HAUPTMAN: It was just initiated. So the screening part of that study just finished.

CHAIRMAN BONE: I see.

DR. HIRSCH: I'm sorry. Can I just make a comment about Dr. Ellis' question?

The experience with obesity drugs is very different nationwide from what happens in a controlled trial. That is, the general experience is these are used very, very broadly and often by small groups who do not follow the recommendations. This is more likely to be the case than with other drugs because of the pressure for getting these, et cetera, a whole lot of things we won't go into, but I think generally we would agree that any stipulations that are set up before treatment are more likely to not take place with obesity drugs than with other drugs.

CHAIRMAN BONE: Further questions or comments from our guests?

DR. SIEGEL: Another question. I realize you had limited serum samples. Did anybody look at prolactin? Prolactin is another one that I, you know, would love to know just to see if in some way it caused an increase.

And then the second question I have is in terms of the racial issue, am I understanding correctly that there were no African Americans in the study? I mean Americans are -- I know the Europeans weren't.

DR. HAUPTMAN: It was about 15 percent African Americans in the U.S. and about seven percent Hispanics or five percent Hispanics.

DR. SIEGEL: Okay, and of the 15 percent -- are any of these 11 patients African American?

DR. HAUPTMAN: No, they're all white.

DR. SIEGEL: So they're all clear. Okay. I just wanted to clarify that.

CHAIRMAN BONE: I think there are a number of other questions and comments or remarks from other members of the Committee if that takes care of our -- oh, Dr. Simon.

DR. SIMON: Well, someone on the Committee had asked previously if you wanted to plan a study how large would it have to be. It would have to dwarf this study by at least -- well, for example, the breast cancer prevention trial, the Tamoxifen prevention trial, which I think is targeting a reduction in breast cancer risk in high risk women, a reduction of probably around 25 or 30 percent. That has, I think, 18,000 women in it.

And so here we're seeing a risk -- you know, we're talking about relative risks of three. We're talking about detecting a 30 percent, you know, difference in the risk of breast cancer. You're talking about, you know, probably a factor of 100 greater than what we were dealing with here.

CHAIRMAN BONE: Well, can we say that without having decided what the relative risk that we wanted to detect was?

DR. SIMON: Well, he had specified the relative risk. He had said that to detect a 30 percent increase.

CHAIRMAN BONE: But on the other hand, if we were going to try to detect a relative risk of three as opposed to .3, it would be logarithmically different, wouldn't it?

DR. SIMON: Right.

CHAIRMAN BONE: All right. Dr. Cara has been seeking the floor and now has it.

DR. CARA: I have a question as a follow-up to Dr. Simon's comment. You seem to really in some ways trivialize the data and didn't appear to think -- I got the impression that you didn't think that it was of any real concern.

DR. SIMON: I certainly would in no way trivialize it. I've gone over it very carefully. I just think that the way that it's being evaluated quantitatively is incorrect, and that you don't start off with saying, well, this is a breast cancer from this drug in this type of setting is totally unexpected, and then you don't sort of get a P value of .05 and then say all of a sudden, "I believe it."

Quantitatively that's not the way you should analyze the data. Quantitatively if you start off by saying what do I believe is the probability before even doing the series of trials, the probability that there could be an increase in breast cancer risk of, say, relative risk of three or more attributable to this drug.

If a priori I say it's one chance in 100, and then I do a series of clinical trials, clinical

trials that are really too small in aggregate to detect a relative risk of three, and if as a result of those clinical trials I get a P value of, say, .05 or .10 for the breast cancer endpoint, and then I go through the proper calculations of saying now what is the probability that the relative risk is at least as great as three, that's not the P value.

It turns out whereas I started out saying that my probability was one in 100, now I would say that probability is four or five in 100.

So all I'm saying is you get a -- if you interpret the data in that way, by incorporating the fact that a priori it was unexpected and that the prior here for detecting such an effect was low, and then if you ask well what is, at the end of it all, the probability that the relative risk is at least as great as three -- this is a Bayesian calculation -- your answer is instead of the one in 100 chance that I started with, it's four or five in 100.

That to me is the proper -- the bottom line answer. Then the question is: well, is five in 100 too great a risk or not?

But to me that's the way to look at it, not to say, well, we got a P of .05 and, therefore, it must be real and it's just a question of whether it's

-- you know, whether we can find some other explanation.

CHAIRMAN BONE: Dr. Marcus.

DR. MARCUS: Well, I'm following your argument, but every so often yo come up with trials that were under powered but scored. For example, the study of hormone replacement therapy done more than two decades ago in 100 pairs of women looking for -- this is by Nochtegal (phonetic) and her colleagues -- looking for changes in incidence of myocardial infarction, osteoporosis, and other endpoints. Anybody who would be planning a study today would say, well, you'll need at least 6,000 women followed over three years to detect fracture. You need to have the women's health initiative to determine myocardial infarction in primary prevention, but there it is.

In 100 pairs of women they showed a significant reduction in myocardial infarction and osteoporosis. Does that change the post probability only trivially? I don't follow.

DR. SIMON: The power of the trial has a lot to do on the posterior -- a lot of effect on the posterior probability. Of course, you're right that important observations can be made in that context, but all I'm saying is the literature is also filled

with erroneous conclusions that came from under sized studies that thought they found a significant effect, and that that latter are much more common than the former.

CHAIRMAN BONE: I think there must be some other comments or questions from members of the Committee. Yes, Dr. Critchlow and then Dr. New.

DR. CRITCHLOW: Well, again, just to address your comment, I mean, I completely agree with you in terms of you're right; the literature is ripe with people doing post study power calculations or post study whatever to make whatever conclusion or hypothesis, but the issue that always has bothered me is in the Phase 3 trials, clearly they're powered for efficacy and not necessarily for safety issues, and particularly for things that are more rare.

And something here is we have essentially what I consider a red herring. The P value, whether it's .01 or .10 or .15 or whatever based on this trial, is irrelevant, but the question is -- and Dr. Marcus phrased it very well -- is this something that we should be concerned about, and I'm not sure a P value is, as you say, an appropriate way to try to judge that.

I mean, clearly our decision on that point

is going to come from the gestalt of things that we think about, you know. How unexpected is it? What, if any, mechanism can one think of?

So, again, given that this is a clinical trial and given that nobody was thinking about breast cancer at the outset, the fact that we have something that has something in the P values or whatever, as they are we're still left with the question of do you totally ignore it or, you know, again, the purpose of this is just to say is there the potential when it's out there in the kinds of numbers that one would need to show it definitively. What do we expect to find?

And, you know, clearly there's no way to answer that.

CHAIRMAN BONE: Dr. New, I think, had the next.

DR. NEW: I guess I was following up on Cathy's comment. What do you think the significance of nine cases of cancer in 747 women treated at random?

I mean, I don't want to hear P values. I want to hear what you think.

DR. SIMON: I don't think this drug is associated with a relative risk of three or more. I don't think that -- I think that this is not -- not

much evidence that this drug causes breast cancer.

DR. NEW: I see, and you base that on the fact that the numbers are too small because it's illogical?

DR. SIMON: Well, I guess I base it on two things. One, on the fact, sort of the quantitative sort of analysis I was trying to sketch out. The fact that it was unexpected, the power was small, the P value was border line translates into a posterior probability of a problem of not a very high posterior probability.

The second thing I guess I base my own opinion on is that I think there is pretty good evidence that some of these tumors -- well, for example, a lot of these tumors were node positive, and they probably -- I mean, I guess we can't rule out that there's some enhancement of growth, but node positive tumors probably existed for, you know -- my basic gut reaction is that they probably existed for quite some time.

DR. NEW: But do you think that the findings should be pursued is the point or do you think it's so epidemiologically, statistically insignificant that it should be ignored?

DR. SIMON: Well, i think that's a

difficult one. I think it could be pursued, you know. I mean, I guess there are several ways it could be pursued.

One, you could do further follow-up on the cases in the randomized studies. I guess you could do some kind of a post marketing type of case control type of study. I guess you could even do a randomized study of 60 versus 120 twice a day in a post marketing type of setting where everybody then would be getting the drug, but you'd have a randomized study in in which -- you know, I don't know whether that's viable or not.

I guess the other way, I guess, it could be pursued is just from a prudence point of view of saying that every woman who gets this drug, she should have a mammogram before she starts taking the drug.

DR. NEW: Henry, could I just continue with one little bit more?

CHAIRMAN BONE: Please

DR. NEW: I'm a pediatrician, and I harken back to the studies of thalidomide, which was that it was tested as a sedative and then proved to cause phocomelia. It was an unexpected finding, and I remember talks of statistical causes of whether the phocomelia could be attributed to the thalidomide or

not, but that turned out to not be necessary because fortunately it was an animal model in which they could show the mechanism by which thalidomide caused phocomelia.

The difficulty I'm having -- and I'm hoping you're going to help me -- is that we don't know the cause of cancer, and I don't have an animal model where at least the animal models presented did not give me cause to believe that this drug induces breast cancer.

One has to be counseled by whether this is a disturbing factor or so statistically abstruse that you shouldn't bother with it.

DR. SIMON: Well, I think I guess my reading of it is it's not a very disturbing factor, but given that the -- you know, there's a very large population who may be placed at risk from taking this drug. If there are -- if there are useful things that can be done to pursue it, that that would be prudent.

DR. NEW: Thank you.

CHAIRMAN BONE: Dr. Ellis.

DR. ELLIS: Breast oncologists all the time spend time with their patients balancing breast cancer risks versus cardiovascular risk because many of my patients after a period of treatment, perhaps

five or six years later, are reconsidering, for example, starting hormone replacement therapy or even see patients who want to be counseled concerning the risk even if they've never had a diagnosis of breast cancer.

So in a sense we're in a similar kind of situation because we have a drug which we will improve cardiovascular risk, but, on the other hand, there's a certain concern associated with breast cancer.

And I was just wondering, to use historical analogies, what the conversation would have been like at the inception of hormone replacement trials where it was not known what the relative risk of breast cancer was, and that became subsequently something we became aware of in the sort of post marketing situation.

So should we deny the benefits of this drug to many women because we're worried about these risks, or should we say we're concerned about this risk, but we don't think it's enough of a risk to prevent the marketing of the drug? However, we need to do post marketing surveillance.

I mean that's the kind of crux as I see it. That was more of a comment, I guess, than a question. I was wondering what the responses were to

that.

CHAIRMAN BONE: Yeah, thanks.

Well, I know Dr. Hirsch had a comment.

DR. HIRSCH: Just two or three points about the risk-benefit ratio, which is really what we're after, and I think one ought to say a word more about benefit, just a brief word.

It's hard to really know what's going to happen, but just judging from other obesity treatments and the nature of this kind of intervention and the data shown, it's possible, even plausible, and I believe even likely -- my own personal opinion -- that within a three to four year period after using this drug, the effect would disappear. It would be the same as placebo for whatever sets of reasons.

This is the trajectory of what we see of the lines of percent weight reduction versus placebo, and remember that we're dealing with about a four percent reduction in weight versus placebo, a very small amount, significant, of course, but very small.

Number two, it's been mentioned, but we mustn't forget that with drug usage or obesity treatment, you are translating this into huge numbers. For example, a very simple calculation shows that if one of the cases that we were shown were drug related,

then what we would anticipate, magnifying this up into what kind of drug usage there'll be and perhaps a three to four ratio of female to male, one might expect an increase in the amount of carcinoma of the breast, if this really is a relationship in one in thousands, in perhaps ten to 20,000 per year, which is a monumentally large figure.

So there's an immense leveraging of this by virtue of the huge potential use of this.

Finally, and I'll stop, I was very taken by the comment about biological plausibility. There is a kind of reverse engineering or reverse genetics that works with clinical investigation. That is, usually when you plan a study, you look for biological plausibility as has been done so ably by the sponsor.

On the other hand, when something like this comes up, there is a reverse thing of reexamining the biological plausibility in terms of other possible pathogenetic approaches that are usually looked for, and what I refer to here is the possibility that something that the drug does so changes gastrointestinal function that agents which might or might not be carcinogenic -- and the National Cancer Institute tells us perhaps a third or a fourth of breast cancers might be related to this avenue, that

is, dietary factors which impinge on tissues -- that might be affected, and the way to examine that is by an extension of fundamental studies, namely, to feed animals different things, different agents that cause malignancy with an without the drug.

So that, you know, like Marshall's observations with H pylori, from time to time observations that are not at all plausible become the most interesting ones.

CHAIRMAN BONE: I just have a question for Dr. Feigel (phonetic) briefly. Dr. Feigel, were the mammograms that you examined just the ones involved with the patients with malignancies?

DR. FEIG: Yes.

CHAIRMAN BONE: Yes was the answer. Thank you.

So there were not a large number of mammograms obtained and then examined to see what the prevalence of similar findings would have been in subjects who did not develop breast cancer in the study. We don't know a background rate of similar findings in this study; is that correct?

DR. FEIG: Yes.

CHAIRMAN BONE: Thank you.

Additional remarks or questions from the

members of the Committee?

Dr. New.

DR. NEW: Dr. Bone, I'd like to ask you a question.

CHAIRMAN BONE: Yes.

DR. NEW: What would be the mechanism by which -- let's say that we think the drug should be approved -- that we could make sure that the women who are prescribed the drug would have a mammogram?

CHAIRMAN BONE: Well, I don't know if I'm the right person to ask the question, but I'm not aware of any mechanism within the power of any governmental agency in the United States, in the states or the federal government to insure that.

Dr. Sobel would be able to answer that question more authoritatively.

DR. SOBEL: We can, you know, make the plea in the label, so to speak, but as far as enforcing it, I know of no mechanism. You know, physicians will use it.

If the state deems that a doctor is practicing recklessly by not doing this, they can have some action, but, you know, it's unlikely.

CHAIRMAN BONE: They would have to pass new regulations.

DR. SOBEL: Well, no, the states, you know, can have judgments in these matters, if they seriously felt this was reckless practice and a physician was violating, but I don't think that they'd have the legal ammunition to do such a thing, you know, based on what we've said.

CHAIRMAN BONE: Dr. Ellis.

DR. ELLIS: I just want to go back to the risk-benefit analysis, and the thing I don't have a good handle on is whereas although I understand that the reduction in weight is not large, there was a number of other cardiovascular risk factors that were mentioned, such as reduction in blood pressure, change in lipid profile, and of course, we don't have a study yet, which is a prospective study, looking at the value of this drug in reduction in cardiovascular risk.

And I was wondering whether there was any way we could calculate the potential value of this drug in reduction of cardiovascular risk.

DR. HIRSCH: They're small, but meaningful, but what I'm saying is they'll vanish in three to four years. That has to be taken into consideration. That would be my guess.

DR. ELLIS: Okay. Perhaps they'd like to

respond to that.

DR. HAUPTMAN: Yes. Could I have Slide S-5, please?

Not all patients who take orlistat are going to benefit as much as other patients. I'd like to show you some data for patients who were on the drug and at the end of two full years of treatment lost at least five percent of their body weight.

CHAIRMAN BONE: Now, this is new data you haven't already presented. Please be very concise.

DR. HAUPTMAN: Okay. Very concise.

Take a look. Those patients on the bottom, and I can't see very well, but those are patients who lost at least five percent at the end of two years. The patients on the top curve on orlistat lost less than five percent.

For those patients who were able to lose at least five percent of their weight, not only did they lose that weight, but they kept it off for two full years.

So when you look at people with regaining weight over time, we have a mixture of those who have not lost weight and those who have lost weight.

PARTICIPANT: What's the number?

DR. HAUPTMAN: I can't -- okay. It's 386

patients in the top group loss less than five percent, and 224 patients on the bottom group. So there are groups of patients who lose weight and keep it off.

Don't mix up the mean effect with the effect of those people who do respond, and that's the only thing I'm asking.

CHAIRMAN BONE: Thank you.

Dr. Marcus.

DR. MARCUS: Just one point of clarification of something. Carcinoma of the male breast accounts for one percent of all carcinomas in men. We had men in these studies. Were there any instances of breast cancer in the men?

DR. HUBER: No.

CHAIRMAN BONE: All right. Are there further questions, specific questions?

(No response.)

CHAIRMAN BONE: Well, what we've done in that past at this point is to sort of go around the table and have anyone make remarks about what they -- you know, sort of their own concluding observations, and then I think we can go around and vote on the questions unless there's something else that we need to attend to before doing that.

Perhaps we'll start with Dr. Simon and

then just go right on around and I'll speak last.

DR. SIMON: I don't have anything to add to what I've already said.

CHAIRMAN BONE: Thank you.

Dr. Ellis, do you have anything to add?

DR. ELLIS: I just emphasize that particularly in overweight women there is a problem with breast cancer detection, and even if a recommendation for -- that because larger breasts are difficult to examine, and they're also more difficult to conduct a standard mammogram.

And if a recommendation for mammography and physical examination was even partially effective, it may achieve an important goal in general, which is to increase the rates of breast examination and mammography uptake in the general population.

So my thought if this becomes a conduit for better uptake for breast cancer prevention in general, that might be a good thing.

I know that not a generally relevant, but it's a practical issue.

CHAIRMAN BONE: Dr. Siegel.

DR. SIEGEL: I think I understand the benefits of this drug, and I'm very impressed with the amount of research that has gone into it and the good

job of presentation done today by the sponsor.

I still don't have a good sense of the risks, and I think that we need to. Breast cancer is too important a problem to say, well, we'll make a recommendation for mammography and then leave it at that.

We know how drugs are used once they get into the public, and there are a lot of people that are overweight that, you know, need treatment, and that's not to understate those problems, but you know, I see a lot of breast cancer. Breast cancer kills people, as well, and you know, I'm not certain that it causes breast cancer, but I'm not convinced that it doesn't have something to do with it as well.

And I think anything that we do should involve some way of getting that answer, of, you know, what is the risk of breast cancer.

CHAIRMAN BONE: Thank you.

Dr. Marcus.

DR. MARCUS: I feel very fortunate to have had a chance to hear absolutely wonderful opinions from people whom I consider imminent authorities in their field, from Jules Hirsch on my left to Dr. simon, and from the statisticians and the pathologists. Everything today has really been first

rate.

I'm persuaded that there is probably no chance whatsoever of doing a properly controlled prospective clinical trial to answer this question just by virtue of the power considerations alone that have been gone over and I won't repeat.

I think that if we take the example of Tamoxifen, which as an anti-estrogen at the breast and is even being used in primary prevention in very large clinical trials, even if that were to show the benefit that one expects, the clinical experience now after five years of Tamoxifen of a reappearance of breast cancer risk is something that one could never in a million years have predicted in advance.

Therefore, I think the only solution to this if one is going to try to maximize in some way the beneficial aspects that this preparation offers to at least some patients is to develop an intelligent, highly sensitive surveillance mechanism that if not foolproof at least is very effective with lost of incentives for people to pursue that.

Now, whether that means the company should offer a free mammogram or whether, as in the case of some anti-psychotic medications where there is a real problem with blood counts, that as part of the

condition of prescribing the drug the physician and the patient agree to undergo periodic, regular and frequent determinations of leucocyte count -- I mean, I think one could build into it. There's a lot of creative people involved in this endeavor both in the agency and from industry. I think some sort of effective surveillance could be developed.

CHAIRMAN BONE: All right. Dr. Molitch.

DR. MOLITCH: I'd like to thank Dr. Simon for reminding me that Bayesian analysis really is the appropriate way to look at some of this data. I must say I never did get an answer to my question about breast biopsies.

Has the sponsor been able to find out?

PARTICIPANT: We couldn't find it.

DR. MOLITCH: And, again, I think that it will deal with risk-benefit ratios that sometimes either we have to deal with or the patient has to deal with in consultation with the physician.

CHAIRMAN BONE: Dr. Cara.

DR. CARA: I would like to just echo some of the remarks by Dr. Siegel in terms of what the breast cancer represents. I think that our tendency is when we talk about issues related to cancer to become somewhat numb to what we're really talking

about, and I think that's very true for breast cancer.

And I can't help but think that if we turn things around and talked about leukemia or talked about prostate cancer, something else that would be analogous to this, whether or not we might be more sensitive to those issues.

CHAIRMAN BONE: Dr. Hirsch.

DR. HIRSCH: I have very few other comments, except one. The field of obesity and energy metabolism, energy regulation has changed startlingly in just the past few years. Whereas ten years ago any kind of new agent or idea that came along in a disease that's so prevalent and so difficult as obesity would have been accepted with open arms.

One becomes less likely to do this with the knowledge that a tremendously increased amount of information about this whole field is very, very rapidly developing. I have a feeling that this will ultimately be transduced into some kinds of more definitive studies of obesity and possibly even very novel pharmacologic approaches.

So we're not in a statis area. That is to say that this is not the last chance.

CHAIRMAN BONE: Thank you.

Dr. Sherwin.

DR. SHERWIN: Well, I don't have too much to add. I just point out that treatment of obesity is a lifelong problem, and if this drug is effective, it will have to be used for life unless something else comes along. That's what you're prescribing. You're prescribing five, ten, 15, 20 years or whatever.

And I don't know what the relative risk of breast cancer is. I think that the data is inconclusive and is extremely difficult to interpret.

So I think that one has to balance a lifelong treatment and an unknown risk, and you know, we'll have to make that decision.

CHAIRMAN BONE: Thank you.

Dr. New.

DR. NEW: I would like to just reaffirm Dr. Marcus' points. I think that any drug that offers weight loss is probably going to be used widely by many people, and I would like some assurance that there would be continued study of this unexpected result so that the prescription of that drug is not delivering a significant number of people a death sentence.

And so I would like -- that's why I asked the question about how you can enforce mammograms. I don't know, Bob, if there were a way to do the very

things you're saying, which is to make a quid pro quo with every prescription. You can't have this drug unless you have a mammogram.

I'm told that that's probably not likely.

CHAIRMAN BONE: Thank you.

Dr. Critchlow.

DR. CRITCHLOW: Well, I don't have anything else to add other than I was struck by the numbers you provided on the Swedish study that 18 out of 2,400 had preexisting mammographic abnormalities, which is about identical to the rate of cancer discovered in the 120 milligram dose, about 1.3 or four percent.

I just do have one question, and that is among women less than 45 years of age there were no cases in any of your extended database, anything having to do with any reports of breast cancer in women under 45?

DR. HAUPTMAN: No cases were reported.

CHAIRMAN BONE: Right. I think that's all of the other Committee members except myself to make remarks, and then we'll proceed to voting.

The medication we're considering is one that appears to be fairly effective in producing weight loss in a subset of patients, although when the

trial group as a whole is looked at, it's only modestly effective and did not reach the primary criterion for approval. It's one with a fairly high rate of unpleasant GI side effects, but not serious side effects.

These are side effects that may be embarrassing or annoying, but many of the side effects described are not the sort of thing that we would regard as producing illness in the patient.

Over the course of the study, we saw modest effects on fat soluble vitamin absorption and retention, which presumably could be addressed by co-administration of a multivitamin preparation, although we haven't heard a specific recommendation about putting these all int he same capsule or something equivalent to make sure that that was done.

An interesting observation was made of hyperoxalurea and the question of some increase in risk of urolithiases was raised, although this hasn't turned out so far to be a major clinical problem.

And there was a finding of increased biomarkers of cell proliferation in the stool, which over the course of the trial wasn't associated with any increase in risk of colonic malignancy.

The major issue that we're trying to sort

of balance in with this perhaps modestly favorable risk-benefit analysis, not considering the breast cancer, is this unexpected finding of an increased relative risk of breast cancer in the subjects who received the test drug.

I quite take Dr. Simon's point that this by no means convicts the drug of causing breast cancer. I'm not sure that's the question, however. I think it's a question for the Committee members to consider whether the probability is so low that it's exculpatory. How confident can we be that this did not increase the risk of breast cancer?

We have some biological information from the toxicology studies. We were told that mechanisms of carcinogenesis which have been proven in drugs used in man have always been reproduced in animal studies.

But I think in this case we looked under the wrong lamp. The mechanism of action of this drug is related to the production of fat malabsorption, and the fact that studies don't reveal a direct carcinogenic effect of the drug on breast tissue or other tissues really don't address the question of whether an indirect mechanism related to, you know, any number of substances which we could imagine being absorbed or not absorbed from the gut.

I think that members of the Committee will want to reflect on, you know, how they weigh this level of concern. We're told that the histological findings are not typical of what one might expect from an ideal carcinogen, if you can put it that way, but, on the other hand, the pattern is not very different from what we've seen in patients who have an increased risk of breast cancer from estrogen or in the excess cases attributable to estrogen.

The question then, I guess, is, you know, sort of what are we going to do about this, and at the end part of the question has to do with how would we go about trying to resolve this in the safest way for the millions of patients who would likely be exposed to this drug and probably for a long period of time.

We're not talking here about something that's given for a few days to cure bacterial meningitis. We're talking about something that incrementally affects a chronic illness and is expected to be given for a long period of time.

And I think the question of whether a prospective trial could be conducted which would give some assurance about this depend very much, indeed, on the relative risk that goes into that calculation. What level of excess risk are we trying to detect?

And we've had a spectrum here of at least one logarithm difference between one proposed level of sensitivity and another, which would more closely approximate what we've seen in the aggregated data from the clinical trials.

So I think these are all of the factors I'll be trying to weigh as I decide what to vote about here, and I just can very shortly start the voting.

I just will have to explain one or two things about the voting. We're very grateful for the participation of Dr. Siegel and Ellis, but if I understand correctly, as guest experts they will not vote.

Dr. Simon is a member of another committee and will be sitting as a member of our Committee today and will vote.

The custom is to go around and take everyone's vote. Everybody has had remarks. So I think we'll just ask people to say yes or no and then if they have an additional remark to make at the very end, we can have an opportunity for that.

And unfortunately Dr. Davidson had to attend to a patient care related matter and had to leave, and we do have his written vote; is that right? And that will be mentioned last in each round of

voting.

So if we would start then with Dr. Critchlow then in the first question, and I'll just read that for everyone.

The first question is: taking into consideration the overall benefits and risks of orlistat, including the increased incidence of breast cancer in the controlled clinical studies, do you recommend that the drug be approved for the treatment of obesity?

DR. CRITCHLOW: I'm going to vote yes for those 20 to 25 percent of patients that might benefit. I'm also assuming that after three or four or five years when the drug may or may not continue to be effective, that people will stop taking it.

CHAIRMAN BONE: So that you're voting yes.

Dr. New.

DR. NEW: I would like to vote yes, but I do -- I would be very anxious for there to be certain warnings and requirements and a post marketing study, such as a baseline mammogram.

CHAIRMAN BONE: Thank you.

Dr. Sherwin.

DR. SHERWIN: No.

CHAIRMAN BONE: Dr. Simon.

DR. SIMON: Yes.

CHAIRMAN BONE: Dr. Marcus.

DR. MARCUS: Yes.

CHAIRMAN BONE: Dr. Molitch.

DR. MOLITCH: Yes.

CHAIRMAN BONE: Dr. Cara.

DR. CARA: No.

CHAIRMAN BONE: Dr. Hirsch.

DR. HIRSCH: No.

CHAIRMAN BONE: The chair votes no.

And for Dr. Davidson?

MS. REEDY: Dr. Davidson votes no.

CHAIRMAN BONE: Dr. Davidson's vote is no. I don't know the count here.

MS. REEDY: Five to five.

CHAIRMAN BONE: Five to five. Well, we settled that for you after a long day's work.

(Laughter.)

CHAIRMAN BONE: This will mean that the actual people with regulatory authority will have taken our advice and had all of our considerations and will have to make the exact same choice that they would have regardless of our vote on either side of this.

I think this is a wonderful illustration

in a way of the fact that the Advisory Committee advises. It doesn't decide anything. The authority is always left with the Food and Drug Administration, and I think is an interesting example of a great deal of advice.

(Laughter.)

CHAIRMAN BONE: The next question, if I can just read that again, and we'll start the other way around this time, says: if orlistat were to be approved for the treatment of obesity, do you recommend that any further studies be conducted after approval to address the breast cancer issue?

And we'll start then with Dr. Simon.

DR. SIMON: Yes, I believe some kind of study should be instituted. Exactly what they would be, I think, would take some more detailed thought, but I think whether some type of post marketing surveillance, study of some type should be undertaken.

CHAIRMAN BONE: Thank you.

And I think at the end of this round of voting we can maybe ask for comments from our guests if no one objects.

Dr. Marcus.

DR. MARCUS: First I'd like to say that the response to Dr. New's question, certainly in the

case of alendrenate (phonetic), the insurance industry has made damned sure that patients undergo bone density testing before they will pay for alendrenate. I think that there are precedents for imposing fairly rigid criteria, and I would certainly support that, and I think that the most rigorous and stringent of post marketing surveillance studies would absolutely have to be done, and it would have to be done in the development of it with the guidance of FDA as well.

CHAIRMAN BONE: So, Dr. Marcus, you're appealing to a power far mightier than the federal government, namely, the insurance industry?

(Laughter.)

CHAIRMAN BONE: Dr. Molitch.

DR. MOLITCH: Well, I would certainly recommend that a pretherapy mammogram be done just like I would never prescribe hormone replacement therapy without being sure that the patient had had a mammogram and a Pap smear done before doing so. I think the same ought to be insisted for this medication until we have further data.

And I also would like to see a very carefully constructed post marketing surveillance with mammography done at intervals to be sure that this is, indeed, safe.

CHAIRMAN BONE: Thank you.

Dr. Cara.

DR. CARA: Well, I would like to see what the results of the European studies show, especially because of the fact that they've been able to obtain prestudy mammograms.

But along the same lines, I would also recommend that some sort of post marketing surveillance study be done with frequent monitoring of mammograms.

I would also encourage the sponsor to do some more animal studies and try to potentially elucidate maybe not so traditional mechanisms by which there may be an effect of Xenical on tumor induction.

I know that proving a negative is very difficult, but at least looking at some potential alternatives I think would be worthwhile.

CHAIRMAN BONE: Thank you.

Dr. Hirsch, the question of additional studies.

DR. HIRSCH: Since everyone makes a little side comment, I'll just point out that in most instances insurance companies are not involved with obesity treatment and will not pay for it by and large over the country.

Secondly, this particular group of patients happen to be because of the socioeconomics and psychologic factors least likely of any other groups to engage in special measures and additional monitoring of this kind.

I'd have to vote yes because clearly if unfortunately this did come to the public, I think it would be very important to do these things.

CHAIRMAN BONE: All right. I'll speak last again.

Dr. Sherwin.

DR. SHERWIN: yes.

CHAIRMAN BONE: Dr. New?

DR. NEW: I think that there was a suggestion made earlier that perhaps the sponsor could offer a free mammogram, and that might be one way to take these patients who might be in the lower socioeconomic brackets to have it.

And, secondly, I don't know whether it's possible, Dr. Sobel, but I'd like to hear a report in a year as to what's happened.

DR. SOBEL: What would you want us to report on?

DR. NEW: I'd like to know about the accomplishments of a post marketing study.

DR. SOBEL: You mean whether one has been organized or --

DR. NEW: Whether it's been organized, what the results are, what's happened in Europe.

DR. SOBEL: I see.

(Laughter.)

DR. NEW: Okay. Thank you.

CHAIRMAN BONE: Dr. Critchlow.

DR. CRITCHLOW: I think definitely something should be done. I have to say I am not unconvinced that there is no breast cancer risk. In fact, I would have to say that I'm sure there probably is some excess risk.

I think the only thing I would add is that if it were approved, that there be some attempt made either labeling or otherwise to educate not only the providers, but certainly the women that would be wanting to take this drug, and let a woman at that point decide whether that risk was worth taking.

CHAIRMAN BONE: All right. The chair would certainly be in favor of further studies of a very rigorous and extensive nature.

The third question is worded: if -- oh, I'm sorry. Excuse me. Yes, Dr. Ellis, your comment on post marketing studies or additional studies if the

drug were to be approved.

DR. ELLIS: I think what we just heard echoes my earlier comment that it's mainly to more mammography in a particularly needy group, and I think Dr. Hirsch's comment is well taken, that this may be a group for which mammography is not a routine matter.

And, of course, the post marketing surveillance will, if it took place, would be very helpful in answering this very important question.

CHAIRMAN BONE: Right. Dr. Siegel.

DR. SIEGEL: Yeah, I think women in their 40s, late 40s should have a mammogram every year anyway. So I definitely would answer an emphatic yes.

I'd like to add that I think it would also be important to have not only mammograph done not just before starting a drug and after, but also to do clinical examination; that mammography is not foolproof by any means, and I think that, you know, including in the recommendations a suggestion that there be a good clinical breast exam by an experienced clinician be added to the annual mammography, and I think absolutely we should do that and collect the information.

CHAIRMAN BONE: Thank you.

And Dr. Davidson's vote on this was?

DR. REEDY: Continued surveillance plus an expanded minority population in new trials.

CHAIRMAN BONE: That I take to be a yes.

The third question I'm going to take the liberty of rewording slightly. It says, "If you recommend that orlistat not be approved," and I think in the second question the premise was if orlistat were to be approved. I think the third question we should construe to mean if orlistat were not to be approved.

If it were not approved at the present time for the treatment of obesity because of concern about breast cancer, what additional study or studies should be conducted to investigate further the association observed in the clinical trials of the drug with breast cancer?

And perhaps we'll start with Dr. Critchlow.

DR. CRITCHLOW: Well, I'm intrigued by Dr. Bone's and Dr. Hirsch's recommendations for additional animal and other preclinical work to directly more target the presumed mechanism by which either through malabsorption or something on that order that would occur.

If it were not approved, I think I would

consider going back and retrieving mammograms that might be available from women in the study. I think I might also expand efforts to go to the women that were under 45 with a similar survey that was administered to those over 45.

I also agree with Dr. Marcus and Dr. Simon that additional preclinical or Phase 3 clinical trials that would be designed to try to elucidate such a breast cancer risk, if it, in fact, were there, is probably somewhat more than what could be accomplished at this point.

CHAIRMAN BONE: Dr. New, if the drug were not approved, what studies should be conducted?

DR. NEW: I think that it would be important to go back and do mammograms on those women who were on the 120 three times a day who had not had a mammogram before to get a better ascertainment of the risk, of the number of women who develop breast cancer because the fact that you say the others didn't, what's the proof of that? That they haven't developed a tumor that they can palpate? After all, if they all haven't had mammograms, how do you know they don't have cancer?

CHAIRMAN BONE: Thank you.

Dr. Sherwin.

DR. SHERWIN: I don't have too much to add. I agree with preclinical studies with known carcinogens that might increase the risk of mammary tumors, and personally I'd like to see another Phase 3 study only because even though it probably wouldn't detect a very high rate, if it detected a similar rate as we see here, I mean, we would all be concerned at that point.

And so because of that, that's what I would have liked to see.

CHAIRMAN BONE: All right. Thank you.

Dr. Simon, I think. If the drug isn't approved, what would you think should be done to settle this or address this question?

DR. SIMON: I would think the only thing that would address it would be a clinical study, clinical trial, and I think one would have to go through the calculations of what size, and I think it would have to be an adequately powered clinical trial because otherwise if you didn't find an effect, you really wouldn't be able to conclude anything. It think it would involve then negotiations in terms of what size effect would be satisfactory to target.

It would have to be a substantial effect. I think the only thing that would be practical would

be to demonstrate in another clinical trial, in probably a larger clinical trial that a very large effect did not seem to exist.

CHAIRMAN BONE: Thank you.

Dr. Marcus.

DR. MARCUS: I certainly support Bob Sherwin's idea of another clinical trial with effective screening of people prior to enrolling in the trial.

And I'd also like to make one other point. In follow-up to Maria's question of getting the surveillance study in effect so that there would be one year from the date of approval, there could be some report that could come back to the Committee. I would say that the contingency on approval would have to be that the agency and the company had in place at that time the surveillance study ready to go, not that over the first year things would be happening to develop and then a year later we could learn whether a study had been organized or not. That's not good enough.

It would have to be ready to role with the first day of a drug launch.

CHAIRMAN BONE: Yes, thank you.

Dr. Molitch.

DR. MOLITCH: I suppose one possibility would be to get some of these stool samples and send them to Dr. Colman for a helicopacter (phonetic) analysis.

(Laughter.)

DR. MOLITCH: But I think more realistically if we look at the Scandinavian studies, at the 2,000 patients that are being done there, and if they're followed up very carefully since that study is already underway with appropriate mammography, that might give us some suitable information.

I think it's going to be very difficult to mount a large enough study to prove a negative.

CHAIRMAN BONE: Thank you.

Dr. Cara.

DR. CARA: I agree with those comments. I think that doing a prospective study is going to be very difficult because of the scope of the study. However, I think that additional preclinical studies might point the sponsor in a specific direction that may be worth pursuing. Getting as much information as they can from this present trial or the present trials that they talked about, as Dr. Critchlow suggested, doing some preclinical studies, looking at the results from the European studies, and then proceeding

accordingly, I think would make sense.

CHAIRMAN BONE: Dr. Hirsch.

DR. HIRSCH: I guess the fact that I said no to the first question sort of means to me the importance of doing studies on this, not abandoning all hope with the possibility of using this or other agents, and I think the preclinical or animal studies are important.

I'm not so barren or bleak as all of you are about the utility of Phase 3 studies that will not have to have, you know, 20,000 people or something of that kind. I think others can be devised.

And one of the important things is unfortunately these patients were not randomized, not for any fault of the sponsor, but just because of this unusual event that occurred, it appeared, and even early in the study, so that it will be very careful to prescreen, perhaps even watching people for six months or a year or something like that or having repeat mammograms before putting them into the two arms of the study.

CHAIRMAN BONE: Did Dr. Davidson have comments on this?

MS. REEDY: A new clinical trial or a new study with mammograms pre and post study and during

study to monitor events.

CHAIRMAN BONE: Yeah, I would like to also have here the comments of Dr. Ellis first, please.

DR. ELLIS: Well, it sounds as if we already have a trial design ongoing in Sweden with pretreatment mammogram which screened out, I think, a number of patients who had preexisting abnormalities, and presumably in that design there's going to be subsequent mammography.

The question is is the 2,000 patient number in that trial sufficient for the purposes of the Committee or is it too small, and we could leave that question to the statisticians.

CHAIRMAN BONE: Okay, and Dr. Siegel.

DR. SIEGEL: Yeah. I mean if we did it, do it right, and that includes all that's been said about the annual mammography and before and after. Also I want to put in another plug for at least annual, if not semiannual clinical breast exam.

And finally I'd like to ask, you know, we have other patients that have been on this drug, the Phase 2 patients that haven't been surveyed, and perhaps there's important information that could come from them as well.

CHAIRMAN BONE: For my part, I think, as

Dr. Hirsch said, implicit in my negative vote on the first question is a strong yes vote on the third.

I think the first thing that would need to be done is to sit down, as Dr. Stadel said, and develop a family of curves looking at what the tradeoff is between the sample size and the effect size that one is trying to detect, and that may be very helpful in making that kind of plan on a practical basis.

But I think that there's a substantial question about whether the sponsor's interest, as well as everyone else's, wouldn't be served better by a large trial that would generate data quickly considering the gleaning that would occur prior to entry.

So that I don't know what the size of that would be. I think that's a practical question, and then people would have to make decisions about that.

It would be a great pity not to have the drug available if it turns out that there isn't a problem, but I think the concern is, you know, what if there is, and we've had enough information to, I think, leave some people at least uncertain about that, and that's where this tie vote comes from.

I want to thank the sponsor for doing a

very thorough, I think, and conscientious job of chasing down these cases and being very meticulous, professional, and straightforward in their presentations today.

And I want to thank the agency for a very thoughtful and insightful presentation, as well. I think this is a situation that we all have taken very, very seriously indeed, and I think everyone involved has approached these deliberations with very appropriate level of concern and respect for all of the varying interests that do have to be taken into account. And I particularly want to thank not only the members of the Committee who have served admirably as usual, but our guests who have made an enormous contribution.

To summarize then, the Committee has voted five to five on the primary question of whether to recommend approval, taking all of the considerations into account, and I think probably a more detailed summary at this point is probably not necessary because I think we all understand very well how this balancing of issues was reached. Thank you very much. The meeting is adjourned.

(Whereupon, at 4:10 p.m., the Advisory Committee meeting was concluded.)